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Health Technology Clinical Committee Public Meeting

January 19, 2018

Josh Morse:

Thank you, Dr. Brown. Everybody welcome. So, I'll do a brief presentation about the program and what's on the agenda for today. So, today's agenda, this morning, we will be reviewing and talking about genomic microarray testing and whole exome sequencing. There will be a bit of an update on how the review of whole exome sequencing will actually proceed today and we will, I think, await Dr. Johnson's presentation and some input from the contractor on that second part. Then, later today, we are scheduled to review continuous glucose monitoring, and that would be an update to that. It's a re-review.

So, a few meeting reminders. We do record these meetings and produce a transcript. That transcript will be made available on the Health Technology Assessment website under the meeting materials location there on the Health Care Authority website. When participating in discussions, it's helpful if you can please state your name and use a microphone. Please be conscious that we are recording all activities during the meeting, and we do pause that recording during the lunch break. If you'd like to provide public comment during today's meeting, you can sign up. There's a table located outside that door over there, and you can sign up to make public comments.

So, a bit of background about the program. The Health Technology Assessment program is located and managed out of the Health Care Authority, a state agency located in Olympia. This program was created through legislation, and it started in 2006. It's designed to use evidence reports, and this committee, the Health Technology Clinical Committee, to make coverage decisions for selected medical procedures, devices, tests, etc., when there are concerns around safety, efficacy, or cost effectiveness.

So, multiple state agencies participate to identify topics and implement the policy decisions that are generated from the Health Technology Clinical Committee. They include the Health Care Authority, which operates the

Uniform Medical Plan and the state Medicaid plan, or Apple Health, the Department of Labor and Industries, and the Department of Corrections. Agencies, as I said, will implement the determinations from the Health Technology Assessment program within their existing statutory frameworks.

So, the purpose of this program is to ensure that the medical treatments, devices, and services that are paid for with state healthcare dollars are safe and proven to work. The program provides a resource for these participating agencies that are purchasing healthcare. We work to develop scientific evidence-based reports on the tasks, on the selected technologies, and we provide staff support and facilitate the work of this independent clinical committee, which is made up of healthcare practitioners from across the state.

A very high-level view of how this process works, once topics are identified as proposed topics, they are nominated. They are ultimately selected by the director of the Health Care Authority, and there is a public input process on technology selection. Once technologies are selected, we go through a process of developing research questions, or key questions, develop a work plan, draft key questions are put out for public comment. Once key questions are final, we have contractors, technology assessment centers that develop evidence based reports. Those draft reports are put out for public comment followed by a final report, followed by a public meeting, followed by implementation by the agencies.

So, the calendar for 2018 is here on the screen. So, today, I have described the topics. In March, we have one topic scheduled. It's the Gene Expression Profile Testing for cancer tissue. In May, there are two topics scheduled, surgical interventions for symptomatic lumbar radiculopathy and pharmacogenetic testing for anticoagulants. A July meeting, a brief phone conference meeting is scheduled to complete the work from May. Typically, this committee has a retreat in September, and we have dates held for that. Then we do not have topics yet developed or assigned for the November meeting, which would be the action meeting following May.

So, to participate, the Health Technology Assessment program has a website, and that information is available on this slide and in the meeting materials. Anyone can sign up to receive Health Technology Assessment program email notifications through the Health Care Authority website. Anyone may provide comment on proposed topics, on key questions, draft and final reports, and on the draft decisions. Of course, the Health Technology Clinical Committee meetings are public, and anyone may present comments today on the topics during our scheduled comment

period. There is information about how to nominate a topic for review, again, on the Health Technology Assessment program webpages, and we're happy to answer any questions, myself or program staff if anybody has questions about the program. So, thank you, very much.

Gregory Brown: Okay. Thank you, Josh. I think we are ready to... do we need to approve the minutes then for July?

Josh Morse: We do. So, our previous meeting business for today is the last meeting the committee held with action items, and that would be the minutes from the July meeting. They are in your binders before the first tab.

Gregory Brown: So, I guess any comments or?

Sheila Rege: Sorry. This is Sheila Rege. So, moved.

Seth Schwartz: This is Seth Schwartz, second.

Gregory Brown: We take this to a vote. All those in favor of approving the meeting minutes, aye.

Group: Aye.

Gregory Brown: Any opposed? None opposed. So, it's been...

Josh Morse: Let's check in with Dr. Walsh.

Gregory Brown: Oh, Dr. Walsh.

Kevin Walsh: Aye. Thank you.

Josh Morse: All approved.

Gregory Brown: Okay. Then we can move to our first topic, genomic microarray testing and whole exome sequencing. So, Dr. Johnson.

Shana Johnson: Alright. Good morning, everybody. It sounds like the microphone is working. Alright. So, I'll be presenting the agency medical directors' presentation on chromosomal microarray. Just for some housekeeping, let me see, where am I supposed to point this?

Donna Sullivan: It should be working. I wonder why.

Shana Johnson: The review of whole exome sequencing has been removed from this technology review. The scope of the evidence review was not adequate to address this topic sufficiently. So, we will look at that at a separate time. So, today, we're reviewing the evidence of efficacy and clinical utility of chromosomal microarray when used in children with developmental delay, autism spectrum disorder, and congenital anomalies.

There are multiple factors that prompted nomination of this topic. One, there has been a large increase in utilization. It's increased about five-fold over the last four years from in the Medicaid population roughly 100 per year to over 600 per year. There has been an increase in requests from tertiary care centers, as well as increasing use in community based centers, general pediatrics, neurology, developmental pediatrics. The use of the test is becoming more widespread over a number of specialists. There is also an increase in requests with children that don't meet the definition of global developmental delay. We're seeing requests for kids with behavior issues, learning disorders, children that are one month behind in their developmental milestones. So, it's increasingly being requested for all conditions. It was also requested from a couple of Medicaid medical directors.

I think it's important to note that the Washington Medicaid program covers about 50% of the children in Washington State. So, this policy affects over 800,000 children.

So, looking at the utilization data, you'll see UMPS fairly small numbers. They went from 1 test a year to 16 over four years. When we look at the Medicaid numbers, you see that in 2013, there are about 100 tests ordered. In 2016, there was over 600. The spend for that went from about \$14,000 to over \$250,000 in four years.

So, when we approach policy for medical genetics, we typically go through three steps. Just to kind of frame how we thought about this when we were developing our recommendation, we look at analytical validity, clinical validity, and probably the most controversial aspect of this is the clinical utility question. When the test is used, does it improve clinical outcomes?

I think it's easiest to look at clinical utility through a spectrum. Clinical utility could be anything from change in treatment recommendations, which is hypothetical, or the purest measure of clinical utility is objective improvement in patient important outcomes, and of course, there are multiple intermediate outcomes, as well, in regards to changes in measures of the decisional conflict.

So, next, I just want to do a brief high-level review of the guidelines and the payer policies, just to kind of get an idea of where everyone is at currently. The National Institute of Health and Care Excellence [NICE], their 2011 guidelines on the world of genetics, probably very old, CMA testing should not be routinely done in all children with autism, but only those dysmorphic features or congenital anomalies. The American College of Genetics, however, recommends that CMA replace the karyotype as a first-tier diagnostic test for children with these conditions. The American Academy of Pediatrics and the American Academy of Neurology have similar recommendations that it be used as a first-tier test for children with global developmental delay, autism spectrum disorder, and multiple congenital anomalies.

When we look at the private payer policies, Uniform, AETNA, and CIGNA, are all pretty consistent that they cover the above three diagnoses for testing. AETNA and CIGNA have a few more conditions associated with their policy. AETNA notes when the results of the testing could impact the clinical management. CIGNA is unique in that the testing must be recommended by an independent board certified or eligible medical geneticist, genetic counselor, or certified genetic nurse, and that there cannot be a conflict of interest between the person ordering the test and the lab performing the test.

When you look at Medicaid fee-for-service and Kaiser, both of those policies are similar in that they cover the testing in children with developmental delays or autism when there are associated congenital anomalies, presumably because the yield of the causative variant in that population is higher when those anomalies are present.

So, next I'm just going to briefly go over the main evidence from the report that informed our recommendation. One thing to clarify is what we mean by diagnosis in this report. Developmental delay and autism spectrum disorder are clinical diagnoses. The tests used that we're talking about today is to establish an etiologic diagnosis for whether the patient carries a specific genetic variant. So, the RTI review, which looked at studies from the United States in 2009 or later showed that a pathogenic or likely pathogenic variant in 8% of children tested for any reason, 5% of those tested of autism spectrum disorder.

There is also a Health Technology Assessment by Grant for global developmental delay or intellectual disability. They found a diagnostic yield of 19% and for autism spectrum disorder 12%.

Other papers have noted that the frequency of disease-causing variants is highest in children with moderate to severe intellectual disability accompanied by malformations or dysmorphic features. It's also notable that the general population has a diagnostic yield of 0.7%. So, normal controls, this is an example. It's a biobank from Estonia. They had a pathogenic variant yield of 0.7%. And then, if you look at the Grant paper, you see, as the phenotypes get more severe, generally, the diagnostic yield goes up. So, we get the 12%, 19%, and then 25% once we're taking in dysmorphic features and congenital anomalies.

So, next I wanted to shift to the high level of results on the clinical management and clinical utility found in the evidence review; 27-93% of cases with a pathogenic variant have a change in management. This represented 3.6 to 6.7% of all cases tested. The changes in management could be a specialty referral, you ordered an image, you ordered a lab, or you changed a medication. There were no outcomes measured. I did see... there was one paper that talked about, that it did inform reproductive counseling, as well. So, the clinical utility here is more of an intermediate outcome, I think, is the point of the slide.

The Henderson paper, I felt this was a really interesting slide, because the Henderson paper pointed out what type of clinical action changes that they were seen, and what you see is on the left hand of the column. Those are all indications. The right hand column are patients with neurodevelopmental indications only. So, developmental delay, autism without complex feature, and you can see on that left hand side that most of the highly actionable findings are on the left hand side. And when you read the paper, those with highly actionable findings where you actually specifically changed the treatment were those with congenital anomalies. Those with neurodevelopmental indications, you saw that they got more referrals, more imaging, and more [inaudible].

When we look at the overall strength of the evidence, it is notable that it is rated as very low, risk of bias. I guess I can't read that either. Risk of bias is, findings tended to be inconsistent across studies, and directness and precision were also serious.

The guideline paper's other side to this is that the clinical utility of microarray testing may not be able to show that there is improved objective outcomes, but they do note the value of the etiologic diagnosis to the family, the estimation of recurrence risk for reproductive counseling, and the value of early detection and early intervention.

So, when we look at this, we've got the benefits just stated that need to be weighed out with the potential harms. Harms would include incidental findings which, in this test, I think, was fairly... the chromosomal microarray was fairly low at 0.4%. False positives, which the RTI report said was 0 to 5.8%, which is about the same as the total percent of kids, the 3.6 to 7.6% of kids that you actually do something for. So, those are kind of overlapping, and I would also just like to know that it could result in the over-medicalization of children with mild delays that are still within the normal curve of development. For example, we have seen requests for infants that are 10-months old, and the test is ordered because they were... they started pulling up at 10 months and they should have been pulling up at 9 months, and we know from our other slide that if you order the microarray, you order two to three more tests. So, all of a sudden, you are doing a lot of testing on an infant who is still developing along the normal curve. So, I just wanted to point that out.

So, the point I'm trying to make with that is making sure we're using this test where it's really needed to help the children and not potentially make them and their families go through perhaps more testing than is needed. The RTI report also noted potential discrimination and social consequences that could result. Here is a case of an 18-month-old child in foster care who had mild delays in speech and motor, which is very common in children in foster care, because they have not had the most nourishing early life, typically, and they did a genomic microarray, and that microarray found a deletion in 15Q, and the parents withdrew their application for adoption. Now, here is the part that I think causes a potential harm. According to the NIH Genetic and Rare Disease Information, this deletion is so heterogeneous that some people have no apparent problems from the deletion. Yet, this child is already being labeled and judged because of it. So, I just wanted to point out that potential harm.

So, when we go back to our approach to genetics policy and the chromosomal microarray, analytic validity was considered mostly supported because of [inaudible] certification. Clinical validity, the diagnostic yield overall seems pretty supported. It's got a good diagnostic yield with good specificity and sensitivity. A clinical utility is less supported, especially when you're looking at which kids you're doing it for. The most highly actionable results were seen more with congenital anomalies or dysmorphic features are present. With neurodevelopmental indications without complex features, we saw more specialist referrals, imaging tasks, and labs.

So, the agency recommendations, given all this information, is to cover genomic microarray testing for genetic abnormalities for multiple

congenital anomalies, global developmental delay or intellectual disability, highlighting that I don't know that there is enough information to be doing this test on children with behavioral issues or milder phenotypes, ADHD symptoms, and autism spectrum disorder. Other conditions for the committee to consider would be that targeted genetic testing, if indicated, has been completed, clinical presentation is not specific to a well-delineated genetic syndrome, and the results could be used to impact clinical management. Any questions?

Gregory Brown: So, could we put up slide 19. I just want to clarify here. So, if we look in that left hand column, the middle there, cancer-related screening or surveillance. So, to me, this is purely an incidental finding, because none of these tests are being ordered for evaluation for potential cancer. So, and that's the number one reason for... that's the number one 'reason' for change of treatment. So, our number one reason for change of treatment is an incidental finding. Is that... am I understanding correctly?

Shana Johnson: Well, I wouldn't say it's the number one, but in the solely neurodevelopmental indication, that is the main highly clinical action in that column. So...

Gregory Brown: Oh, so...

Shana Johnson: ...I guess what I'm saying is, I think, in general, you're correct. I don't know if it's the number one, because they also brought a lot of clinical referrals and imaging and labs, but they also had a lot of incidental findings and cancer screens that came up as a result.

Gregory Brown: ...I guess the N, total N is 24, and they have pharmacologic treatment, cancer-related screening contraindications. So, the cancer-related screening is 11.

Shana Johnson: Are you looking at this one or this one?

Gregory Brown: No. The left one. Yes. That one

Shana Johnson: Oh, I'm sorry.

Gregory Brown: Yeah. So, I mean, 11 of the 24 are in that category and actually the second category is cancer-related screening avoidance. So, if you add the two of them, 14 out of the 24 are cancer-related.

Shana Johnson: I think that's a really good point.

Gregory Brown: Yeah. Thank you.

Shana Johnson: I see your name a lot.

Amy Yuen: Okay. A couple of the findings that are listed under the cancer-related screening category are findings that would lead to developmental issues but also have a cancer concern in the phenotype. So, the list has a mixture of different findings there.

Shana Johnson: Thank you.

Kevin Walsh: So, thank you. That is interesting, that point that the left hand column has incidental findings that are both cancer and may be neurodevelopmentally both, but under the right column, the indication was a neurodevelopmental problem, and they detected a cancer risk. So, the action is that those kids have to be screened or watched for cancer-related issues. So, that's an incidental but positive benefit. Is that right? It kind of flips between the two columns.

Shana Johnson: Well, I always get torn on that point, because based on that reasoning, we all should get genomic microarray, because we could all have these cancer genes. Am I misunderstanding that? So, I mean, it's a positive and it's...

Kevin Walsh: It's not a reason to do it, but it is positive.

Amy Yuen: This is Dr. Yuen again. I would tend to agree with your assessment. It wouldn't be the primary reasoning we've ordered it, but once you've found it, now you're making a very positive impact in the child's health. So, particularly, let's say for example that APC deletion, now we know this is a kid who is at high risk for colon cancer, even potentially as a teenager. So, not in an age range where we would have even thought about it. The penetrants there is, this is one of the few cancer syndromes where it's close to 100%. If that kid doesn't get taken care of, they are almost essentially going to get colon cancer. So, now, early screening and management will make an enormous impact.

Shana Johnson: That's a great example.

John Bramhall: Could you, slide nine I'm looking at, this may be asking a lot of you, but can you just unpack that distinction between the NICE recommendation and the American College. So, NICE is the UK agency, which is [inaudible], and the issue is, we're gonna test when there's no dysmorphism versus we're gonna test when there is.

Shana Johnson: Exactly.

John Bramhall: Can you unpack that just a little?

Shana Johnson: If I'm understanding your question correctly, I think the main distinction there is that the chance of finding a causative variant is higher when there are congenital anomalies or dysmorphic features associated with the developmental delay in autism, whereas that chance is lower if those things aren't there. We'll say, and Dr. Yuen, you can correct me, but with the congenital anomalies and the developmental delay, put that number up at, like, 20%, with just pure developmental delay, it might be more, like, 10%. So, some payers, a couple of years ago, and some guidelines, like this one, which is a little older, felt that maybe the benefit, and now I'm kind of... I'm surmising that the benefit/harm ratio was better when you had both of those present. The other issue there is congenital anomalies present and then you have an underlying genetic syndrome present, it's more likely to find a highly actionable finding. Whereas, if you have just autism that's not complex or a nonsignificant developmental delay, your clinical diagnosis and your treatment, for the most part, are going to be exactly the same, whether or not you know what the causative deletion was. So, that's kind of been the separation, or the rub point in policies, is should you be doing it for everyone with those features or just those with congenital anomalies and dysmorphism. That's kind of what that was portraying as 2011 was kind of that thinking. Then, the 2013, 2014, and 2015 guidelines kind of moved to no, let's do it on everyone.

John Bramhall: Well, it's an evolution of thinking perhaps, over time. Is that fair?

Gregory Brown: Well, I don't think it's simply an evolution of thinking in, if I understand correctly, from the contractor that did the review. They didn't look at any studies prior to 2011. So, basically, they said the technology has changed enough since 2011 that they aren't including the older studies. So, if the 2011 guidelines are based on older technology and 2013, 2014, and 2015 are based on an improved technology, then it's not just the philosophy. It's, we now have better technology to find more things.

John Bramhall: Reasonable. And just one... the technology is evolving, though. Is that correct? The range of probes that are used in these tests increases in specificity and range over time, or is it static?

Shana Johnson: I would defer to Dr. Yuen on that. I think she might have higher knowledge.

Amy Yuen: Yes. They have improved dramatically just in the past couple of years.

- Shana Johnson: Thanks.
- Chris Hearne: On slide 6, which is the rate of growth for the two different populations, do we have anything that tells us beyond the cost what outcome benefit for those kids, other than anecdotes?
- Shana Johnson: I think that is the crux of the question here, yeah.
- Chris Hearne: But there isn't objective data? All we can do is look at other studies where...
- Shana Johnson: Right.
- Seth Schwartz: ...where process measures, which are basically, it changed management, but not necessarily any indication that it changed the outcome.
- Shana Johnson: You're correct, and when RTI did their review, my understanding is they did not identify any studies that showed that data.
- Seth Schwartz: Okay. And then, just as a follow-up then, how is this different from clinical decision making around the utility of ordering any test? I mean, why is this not a clinical decision? Why is it an administrative decision? Is it because of the... there's a delta between perception and fact or pressure from families? These are very compelling kids we've tried to do something for, you know? You obviously want everybody to do well. So, what... the driver for this being not a clinical decision is what, in your opinion?
- Shana Johnson: I think you've well highlighted the reason why this topic has been nominated. I hate to put my...
- Seth Schwartz: So, there is a delta. There is a difference of opinion between the data, the objective data, which is limited in terms of outcomes, and the interests of a very invested constituency?
- Shana Johnson: Yeah. I mean, in my experience, which is limited, genetic tests are typically approved when there is more clear clinical utility in the case of nonsignificant developmental delay and autism spectrum disorder, but perhaps it's the potential effect on reproductive counseling that drives it to the other side, because if you look at most of the private payers, they are all covering this. Whereas, for other genetic tests with this level of clinical utility, I don't think they would be. So, there is... that disconnect is there, and it's part of the reason that we nominated it for this committee, because there is a large disconnect between what the ACGME is recommending and what the evidence is telling us.

Seth Schwartz: Thank you.

Gregory Brown: I think for me the missing piece is all these discussions are centered around the balance between false-positives and actual true-positives. So, I don't think you had a slide on it, but I think the report, a 1.7% sticks in my mind, but it may have been 1.3. Anywhere, I thought it was somewhere between 1 and 2% of false-positives.

Shana Johnson: They give a false-positive range of 0.0-5.8%, but within that paragraph, they talked about kind of... you know, there's two types of the arrays. There's the polymorphisms, and there's the other type, and they kind of, they lumped it all together. So, I didn't know if the false-positive... I didn't know what was 0.0 and what was 5.8%.

Gregory Brown: Yeah. I thought there were... I agree. I thought they reported on two different tests, and they're here now, so they can answer. I thought each had a different rate, you know, with a range, but I thought they were both somewhere on the order of 1% or between 1 and 2%. So, if you're... I mean, you know, this is, like all tests, there is significant downside to false-positives and all the workup and procedures and everything that go along associated with that. So, you know, yes. It's great to find out early that a child has this deletion that you can screen for colon cancer, but if you're screening every child for that, the false-positive rate is probably going to dwarf the actual true positive rate, and all the tests and colonoscopies and everything else that you're doing and all the side effects from them. So, anyway, we can ask through that after their proposal, or their presentation.

Shana Johnson: Dr. Yuen, do you have a comment?

Amy Yuen: I'm perplexed by where they're getting this false-positive rate from. It's a very accurate test, and I have not encountered any that I have suspected to be a false-positive. The laboratory that we use for our clinic, we have negotiated with them where they provide a free follow-up FISH study every time for the chromosome array. So, as long as the reason detected is big enough for the FISH to be done, they run a FISH for us for free, and these have always matched up. So, all of our results have been verified, and I haven't had any false-positives on chromosome arrays.

Shana Johnson: That's very helpful, and like you said, the range that they quoted was zero to 6%, which in the world of false-positives is a big range, and I wondered if the newer tests were maybe lower and better, but it wasn't specifically called out. So, thank you for that clarity.

Amy Yuen: The only time I've had any kind of discrepancy was a false-negative and what had happened is, the DNA sample had degraded, and the laboratory running it should have actually called out that it was a poor-quality sample, but they thought it was close enough. So, they called it normal, and on further investigation, it was found out later it was a false-negative.

Shana Johnson: Thank you.

John Bramhall: And I sort of wondered what a false-positive would be, because the situation is, a test is being ordered because of clinical suspicion, and then a result comes back that there is a gene modification. Is a false-positive then defined as one that's not supported by subsequent genetic testing?

Amy Yuen: That would be my suspicion, but I haven't seen that in my practice.

Seth Schwartz: Can I ask a follow-up question? Sorry, on this slide? What we're seeing is, we're seeing, like, a six-fold increase in the number of tests, but a 20-times increase in the cost of that. And so, what I'm curious, did that cost that we're seeing there, the 257,000, is that just for testing, or does that include any of the follow-up management for those kids?

Shana Johnson: So, when I looked at the definition for total dollars paid, that was just supposed to be for the CPT code. Other things that I could tell you that may inform that is, I've looked at some of these reviews and sometimes the bill is \$1000 and sometimes the bill is \$7000, and again, this isn't data. This is just what my eyes have seen, but there's been a large variation in price that I've seen.

Seth Schwartz: But as far as you know, this is just for the testing, just for the CPT?

Shana Johnson: For the total dollars paid, my understanding is that's just the CPT code, and I'm getting a nod from the data person.

Sheila Rege: Sheila Rege here. Early detection is so important, but my question with medical landscape changing with retail health clinics and all sorts of things coming into the marketplace, with the agency's recommendation, what would be the... could every kid get tested because parents want to find out early. They're so scared of autism. They walk through a pharmacy and they say, oh, we'll do it for you.

Shana Johnson: Right. That's why I wrote the word global developmental delay. The word global developmental delay, my understanding, that definition means that they have a significant delay, greater than two standard deviations in two different areas. So, they have a moderate to severe phenotype that's

present, as opposed to just any abnormality. So, that's why I actually called out that language, to draw that there.

Sheila Rege: And I'd be interested in the expert. I mean, should there be that... you know, some of the commercial insurances have getting a medical geneticist involved. Is that... would that be something to be considered, and I, I'm just worried about how things could change.

Amy Yuen: I think that can be very helpful. When we see children, sometimes they just might have a very mild delay or even in the time since they were referred they've had a catchup, and they've caught up with their milestones. We meet with the family, and we go through everything. We assure them and hopefully families feel better at that point. We don't do testing. So, we would want to avoid overreacting and ordering it before it was truly indicated.

Shana Johnson: Anecdotal support to that, I've never had a request come out of a medical genetics clinic that seemed over-reactive, but as the test is being requested from more community based centers, I'm seeing it requested for temper tantrums or one-month behind milestones. And I think that's where the concern comes up in my mind, because children do have a normal variation of development. Would you agree with that, Dr. Yuen?

Amy Yuen: Yes. So, we should always be very cautious and go through things quite thoroughly and determine whether it's truly indicated. The only difficult we may encounter with this is, insufficient genetic services to meet the growing demand. Otherwise, I would love to have them all come if there's a concern, and we can go through and say, no. Let's reassure you. The other important point is that the genetic testing doesn't diagnose autism. Some families have that as a misunderstanding when they're coming into clinic that I'm going to run a test and figure out if their kid has autism, whereas that's a completely different evaluation. So, it's important just to have the clear and accurate information to help these families.

Gregory Brown: I think in light of your comment that there is also regulatory issues of those commercial genetic testing. The FDA has even shut some of them down saying you have not documented that your testing is accurate enough to make healthcare counseling or decisions based on the accuracy. So, I think there probably is a huge variation in accuracy based on whether you're doing this, microarrays versus whole genome testing, individual in a commercial company.

Carson Odegard: To our expert, so getting back to this false-positive discussion. So, as the testing evolves, is there a standardized range that the observer, as the

technician, would be looking at that would, for some reason, cause some subjectivity of the decision that would cause that false-positive. In other words, in this setting, the testing was probably over... there was some oversight that was probably very rigid, but as these labs evolve and, like you say, get into the marketplace, do the values... is it a really tight decision making, or is there some subjectivity involved in those that could probably, possibly lead to a false-positive and also lead to more problems in the future, as some of these labs evolve?

Amy Yuen: The laboratory doing the testing needs to have very rigorous quality controls, so that we don't run into a situation where they're reporting out a finding on a invalidated sample or where the signal did not look clear from their analysis. So, as more labs begin to offer it, they need to be closely monitored and regulated. We need to make sure where are we sending our samples? Are they good, reputable labs that do the quality controls versus a commercial lab that hopefully they're not doing this but they're, maybe, perhaps taking shortcuts to improve their profits?

Gregory Brown: I think in light of time, we should move to our scheduled and open public comment period. We can certainly address further questions after our other presentations. So, I think I saw one person scheduled.

Josh Morse: We have, yes. We have one scheduled commenter, Jesse Contra, and one signed up this morning, Julie Simon.

Gregory Brown: Okay.

Jessie Conta: Good morning. Thank you for the opportunity to testify today. My name is Jessie Conta. I am a board certified licensed genetic counselor. I am representing Seattle Children's Hospital and PLUGS, which is a national laboratory stewardship collaboration whose mission is to improve test ordering, interpretation results, retrieval, and reimbursement. Really, just to help guide laboratory stewardship efforts across the country, which I think is a really important point to make regarding the conversation we've been having.

So, first, I'm really pleased to see that the scope of the review to include the analysis of both microarray and whole exome have been modified. The evidence in the report was inaccurate. The technology for whole exomes is really inappropriate to use to detect chromosomal abnormalities. So, I'm relatively sure that that will be separated. We actually know of one national payer who already saw your evidence and was using it inappropriately to make decisions about [inaudible] utility of whole exome sequencing. So, I'm glad that will be tabled for another time. Regarding

chromosomal microarray, I think there's great clinical and analytical validity and evidence that's been presented today. There is certainly a challenge in terms of clinical outcome data, and that's true across genetic testing. I think a broad policy, as described by Dr. Johnson, she did a great job of that, is really helpful, but the challenge will be those nuance cases that she described. So, I would argue that implementing a policy, in addition to having a practice for utilization management in a laboratory to ensure that [inaudible] has reviewed those requests and weeds out tests that don't make sense. So, in our hospital, that's our process. We have a genetic [inaudible] who can [inaudible] whether or not the test is really [inaudible] makes sense, and if it's not, then we don't do it, and we provide guidance on why that's the case. So, I hope that, you know, this discussion today will lead to productive coverage of this test, but also in a responsible way that ensures that really only [inaudible] is coordinated, because we should only be paying for the things that will make the most impact. So, thank you, very much, for the opportunity to speak.

Gregory Brown: Thank you.

Tony Yen: Before you leave, could I ask a question, please?

Jessie Conta: Yes.

Tony Yen: So, if we were to, and this was going to be a follow-up question for me, based on the CIGNA and Kaiser policies, which have an oversight role, similar to Children's. If we were to think about something like that, is there the genetic counseling capacity in the region to handle the volume at the rate that it's growing?

Jessie Conta: It would have to be done carefully. There certainly would be [inaudible] if the requirement was to be evaluated by a medical geneticist or genetic counselor. In our role, we don't meet with the patients directly for an assessment of records and a conversation with the provider, and that can be done in a more broad way. There are services through Children's and others who are doing this type of remote utilization management review that would be effective at a case spanning the services that are limited but provide the expertise that would be necessary to implement this effectively.

Tony Yen: So, that's a remote consultation. Is that paid for, I mean, is that a paid service, a consultation service that we would include as a separate fee?

Jessie Conta: Potentially. You know, I think it already exists in many places. Many labs are already doing this. So, it's something that certainly [inaudible] Seattle

Children's, you're already getting this, [inaudible] being tested or [inaudible]. And others are starting to do the same, but the details would have to be sorted out, but I think that the advantage of the... the return on investment on something like that would be great, because you would be able to get rid of a lot of waste for stuff that's not appropriate.

Gregory Brown: I'm sorry. One follow-up there. If I heard you correctly, you're not just saying this test is inappropriate if you feel that there are other tests that are appropriate, you're also making that suggestion?

Jessie Conta: That would be a conversation. That's correct.

Gregory Brown: Alright. Thank you. I think our first public speaker, I think there's a three-minute limit, just to clarify. I didn't do that the first time, but thank you for following that.

Julie Simon: Well, thank you for this opportunity. I will keep my comments brief. I promise. So, my name is Julie Simon. I am also a board certified licensed genetic counselor in the region. I've been practicing genetics for seven years now, and I work for Genetic Support Foundation, which is a nonprofit genetic company that's actually based down in Olympia, and we are trying to address that question that was brought up for the last commentator. So, I appreciate the opportunity to provide some feedback, and our main goal, it sounds like, is your main goal. We want to make sure that the right test is being ordered for the right patient at the right time, and with the initial technology review that had come out, we had some concerns about the broad impact, and I was very happy to see that you had removed the whole exome sequencing from this discussion. The microarray is appropriate in many cases, and there are a lot of nuances that need to be addressed that we would have concerns if it's kept in its current state, would limit some of those patients who do have appropriate indications that don't fit into those boxes. So, I think the continuing conversation with the providers to get the appropriate children to get the appropriate test and make sure it's being interpreted appropriately for their care is important, and I'm glad to see that you're going that direction. There are guidelines. There are providers who have the expertise to get this done for the patient. So, we'd like to see keep pulling that in for these patients to make sure that they're getting testing appropriately, and it's not being abused or over-ordered, but it's getting done at the right time. So, thank you.

Gregory Brown: So, just for my understanding. You said that there would be patients that would fall out of this. So, the state has recommended developmental delay, intellectual development, multiple congenital abnormalities, or

autism spectrum disorder. Are you saying there's patients that should have this testing that don't meet those four criteria?

Julie Simon: There's patients that could. We want to make sure that we're open to getting those covered when it's appropriate. These are beautiful guidelines and are able to catch a whole lot of them.

Gregory Brown: Right. So, can you give me an example of someone that would fall outside of that? I mean, there's always someone that could, but, I mean, without a concrete example, it's hard to make a policy decision.

Julie Simon: Well, I've seen, families who have, or have some mild intellectual disabilities with mild congenital anomalies that wouldn't fit into that multiple congenital anomalies with severe or moderate to severe intellectual disability, and there's just not the, the written data to support or show those examples that you're looking for. So, they're good. We just want to make sure we're not pigeon holing patients that could fit.

Gregory Brown: Okay. Thank you.

Julie Simon: Thank you.

Gregory Brown: Okay. Any other, oh.

Josh Morse: And did you sign up for a public?

Deb Lockingdoyle: I did not, uh, this is, I'm Deb Lockingdoyle with the Washington State Department of Health, and I wanted to get back to a question, because there was a nuance there. I'm not sure what's clarified, and that was the capacity in the State of Washington for genetic services. So, having just completed a wait time study across the state, I will tell you that we do not have the capacity to have every test be ordered only through a board certified medical geneticist, genetic counselor or nurse geneticist. What Jessie was talking about was service utilization, review laboratory utilization. That type of service could easily be done, and that would have the oversight of somebody who is board certified in genetics, and that would be a model that should really be embraced, and would save the State lots of money, but to have every single test have to go through a board certified geneticist would be a bottleneck and would be dangerous.

Gregory Brown: Thank you. Any other local public comments? Seeing none, is there anybody on the phone that would like to make a public comment? Okay. Not hearing any, then I think we are done with our public comments, and we can proceed with our evidence report.

Nedra Whitehead: Thank you. I'm Nedra Whitehead from RTI International. I'm going to start by telling you a little bit about myself. I'm the director of RTI Center for Genomics in Public Health and Medicine. I received my Master's in Medical Genetics in Indiana University, and my Ph.D. in Epidemiology from Emory University. I'm a board-certified genetic counselor, as well, although it's been a lot of years since I saw patients. I was the principle investigator for our Health Technology Assessment on the use of chromosomal microarray and whole exome sequencing and the diagnosis of children with autism, developmental delay, intellectual disability, or congenital anomalies, and I am happy to be here today presenting the results.

I'll try to define terminology as I go. If I don't define something, and you don't know what I mean, stop me and I'll be happy to define it. I wanted to note a few abbreviations that are used throughout the presentation.

I'm going to present some information that will help understand and interpret the information in the report.

So, as a reminder for those of you whose biology classes were a long time ago, chromosomes are your genetic structures, and humans usually have 23 pairs. During the production of an egg or a sperm, chromosomes can be lost, gained, or rearranged, and rearrangements may be balanced, which is what the picture is for unbalanced.

Genomic changes can range in size from the gain or loss of an entire chromosome to the change of a single base pair. Different types of genetic testing identifies changes of different sizes. Karyotyping identifies changes around 3 million base pairs up to entire chromosomes. Chromosomal microarray can identify changes across the genome, as small as 30,000 base pairs, and sequencing can identify changes as small as one base pair, wherever they occur in the genome. That's [inaudible] on the whole genome sequencing.

As this shows, the chromosomal microarray and whole exome sequencing generally identified genetic changes of different size along this continuum.

Gregory Brown: I'm sorry. Dr. Yuen used the term earlier, FISH, and you had it in your slide. Could you explain FISH?

Nedra Whitehead: FISH, fluorescent in situ hybridization.

Gregory Brown: Okay.

Nedra Whitehead: The color things on the earlier slide, basically you take something similar to that and stick it to one particular part of the chromosome.

Chromosome abnormalities occur in about 44 of 10,000 births that survive until at least 20 weeks gestation. Most cases are abnormalities in the number of chromosomes, such as trisomy 21 or Down syndrome or [inaudible] or Charter syndrome. Smaller or more rare abnormalities occur in about 7.4 of 10,000 births. The impact of unbalanced chromosome rearrangement on the patient's health and development varies depending on the size and location of the deleted or duplicated material, and the ileal of any genes for which there is a copy number change. As shown in this illustration of Di George syndrome, which is caused by a microdeletion in the long [inaudible] chromosome 22, deletions often include multiple genes and can result in severe consequences.

Chromosomal microarrays are [inaudible] arrays overlapping or not overlapping probes cover the entire genome. The probes may be [inaudible] nuclear type probes, which detect short sequences of DNA or probes that detect selected regularly spaced polymorphic base fares, or both. As knowledge of which regions of the genome are most clinically significant, array probes are revised target those regions with greater accuracy.

This slide shows the microarray process, although this example uses tumor DNA. The process is the same for any kind of cell. DNA from the patient is extracted, chopped up in small pieces using enzymes and labeled with a fluorescent molecule. DNA known to be chromosomally normal can be used as a control, or an in silico control based on previous test of normal DNA can be used. The labeled DNA is allowed to hybridize to probes fixed to glass plate. And then you wash away the stuff that's not hybridized. If a region of DNA is deleted on one chromosome of the test sample, there's only half as much of the signal there than there would be in a control, and if it's duplicated, there's twice as much of a signal. Those are scanned, and software analyzes how the color intensity or the color changes and call is the terminology used, whether or not there's a copy number variant, a deletion or a duplication.

Whole exome sequencing provides the actual base pair sequence for all the parts of the genome, the code for protein, including the regulatory [inaudible] sections usually. The patient's DNA is again chopped up, mixed with synthetic DNA linker that binds to exon specific sequences and the probe is bound to solid surfaces. The plates are then washed in the DNA mix in the linker with the bound patient exome DNA binds to the probes.

Once the unbound DNA was washed off, only the DNA containing the protein coating regions remains. Each of the small pieces of bound DNA is sequenced and [inaudible] analyzes all the small segments of sequences to determine where the sequence differs from the control genome.

So, both chromosomal microarray and whole exome sequencing identify genetic variation across the genome, not limited to specific regions or specific chromosome. The primary difference is in the size and the type of variation detected. Changes in the number of chromosomes, large rearrangements, and large duplications or deletions, can be detected by karyotyping. Chromosomal microarray can detect duplications or deletions in the midrange, and whole exome sequencing detects small changes. Comments were made earlier, and we received several public comments saying that whole exome sequencing can't be used to detect copy number variant. There's some nuance there. That is, it is not usually used clinically and the software that calls these has not always called them accurately at this point in time, but the actual sequencing itself can detect chromosomal duplications through deletions, as long as they include at least one exome. In some cases, the software is being tweaked and is evolving so that there are cases where the ability to detect those is improving. I wanted to clarify that. It's not quite as cut and dried as it sometimes can sound. After any genetic variants are identified, the laboratory determines if these are likely to explain the patient's symptoms, or not likely of clinical significance if the significance of the variant is unclear, and also if there is a reportable finding that isn't related to the patient's symptoms but has clinical impact. They made the determination by first examining databases of known variants, including public databases of known benign variants, as well as ones of pathologic variants. Also, their own previous test results for children with similar conditions and I... sometimes they call other laboratories and see if anybody else has found the same variant. The likely pathogenicity of the previously unknown variants are evaluated using a variety of tools. Many of them based on the American College of Medical Genetics and the Association of Molecular Pathology guidelines that were published in 2015.

Chromosomal microarray and whole exome sequencing are considered laboratory developed tests in most cases. The laboratories performing the test are regulated under the clinical laboratory improvement amendment standards for high complexity testing, but the tests, themselves, are not regulated by the FDA. However, if a company develops a kit to aid in conducting the test, the kits are subject to FDA premarket approval. To date, two kits have received FDA approval, the Affymetrix CytoScan Dx Assay in 2014, and the Agilent GenetiSure Dx Assay, which was approved in August of this year. The kits are approved for the diagnosis of

developmental delay, intellectual disability, congenital anomalies, or dysmorphic features. Some laboratories use these kits but work with the company that produced the kits to customize the kits for their particular laboratory. The customizations may involve the probes or it may involve the software that is used to analyze the scanning data.

So, Dr. Johnson talked about this in more detail than I am going to hit on, but the topic was chosen because of concerns within Washington about the safety, efficacy, and cost of chromosomal microarray, the increasing number of tests ordered for chromosomal microarray in particular, and several practice guidelines. The increasing prevalence of request for chromosomal microarray and autism and the lack of specific guidelines about the degree of developmental delay, which could lead to many requests for chromosomal microarray at considerable cost.

This was the analytic framework for our review. The research questions were how often the chromosomal microarray or whole exome sequencing return an informative result, what we're referring to as diagnostic yield, or what types of conditions are chromosomal microarray or whole exome sequencing most useful. Does the diagnosis change the child's management? Do children with congenital defects, autism, intellectual disability, or developmental delay who are tested with these technologies have better health outcomes?

These are the PICOTS we used. I'd like to note a few key points. Although the review was focused on children, we did include studies of adult populations with these conditions who had not been tested as children. We have limited our consideration of whole exome sequencing to chromosomal abnormalities, not single chain changes, and we limited studies of diagnostic yield to U.S. studies with testing conducted in 2009 or later.

Seth Schwartz: Nedra, can you explain how our SCOPE led us to remove whole exome sequencing from this conversation?

Nedra Whitehead: Yes. I was getting, just getting to that.

Seth Schwartz: Okay. Thank you, very much.

Nedra Whitehead: So, we limited the SCOPE in order to meet the timeline, and in limiting it, we excluded addressing analytic validity. We did not address the use of these tests in the diagnosis of management cancer, prenatal testing, or other context. Limiting our evaluation of whole exome sequencing to its ability to detect chromosomal abnormalities underestimates the

diagnostic yield and utility of whole exome sequencing, because its primary purpose and clinical use is to detect single chain changes or very small of a few base pairs, insertions or deletions, within a single gene. We did not have sufficient time to include both single gene disorders that lead to these conditions, as well as a chromosomal change in the review, and due to the limitation and the resulting decision that whole exome sequencing is not a policy target for today. I'm not going to present the whole exome sequencing results. Did that answer your question?

Seth Schwartz: Yes. Thanks for helping. Thank you.

Nedra Whitehead: And on that note, we did not consider the impact of incidental or secondary findings either of the negative or safety or ethical issue or as a potential positive of clinical benefit of the test.

Chris Hearne: On your previous slide, the outside the U.S. issue, I have no idea whether the U.S. is the leader, equal with the pack, or behind the rest of the world on this.

Nedra Whitehead: So, we limited it to the U.S. because there were a lot of studies of diagnostic yield that had been reviewed in 2015 by the Blue Cross and Blue Shield, and there was more than we could do. So, we limited to the U.S. because we thought [inaudible] technology is the call for pathogenicity of variants might change, and there's always a small chance that there is a change... a difference actually between the population and other populations. So, we knew the U.S. studies were relevant. We weren't sure about the others, and that was the relatively easy limitation to decide on. We limited to 2009 or later, because of changes in testing technology. As you'll see when I get to the results, we looked at our results, and we compared them to those of [inaudible], which is a Blue Cross/Blue Shield review, and you get a much higher diagnostic yield in the nine U.S. studies. I'll go in a little bit onto some of the things I've looked at about that, but I haven't found an answer yet about what.

So, we searched Medline, clinicaltrials.gov, and the FDA device approval databases. We conducted extensive hand searches of the bibliographies of previous health technology assessments and systematic reviews, and of the excluded article, included articles. A pilot review of 20 titles and abstracts found very high cross reviewer consistency on inclusion or exclusion decisions. So, the remainder of the abstracts were reviewed by a single reviewer, and I reviewed all the citations that were excluded due to testing platform, and a sample of the excluded articles to ensure that the review remained consistent.

Each article was abstracted one and reviewed by me. Two reviewers independently conducted risk of bias, assessment, including a risk of bias instrument approach for the type of study, appropriate for the type of study. We conducted meta-analysis if there were three or more publications with a similar approach and outcome measures.

We retrieved 2912 citations through database searches and identified six by hand search. After title and abstract review, 18 articles were included, one on safety, seven on diagnostic yield, seven on management, and five on cost. No studies of health outcomes were identified.

The limitations on SCOPE also limited considerations of safety. We limited studies of false-negatives or false positives to U.S. studies with testing conducted in 2009 or later, which was the same criteria as we used for diagnostic yield, and we did not find any studies that met that criteria. As previously mentioned, we didn't consider either the negative or the positive aspects of incidental or secondary findings. Within these parameters, we found one study that reported on a safety issue, a chromosomal microarray, which was discrimination based on CMA test results. I'm going to talk about those results, and then I'm going to come back and touch on the earlier discussion about false-positives.

Gregory Brown: Sorry, because you found no health outcome studies in the U.S., did you by chance look internationally to other international studies on outcome?

Nedra Whitehead: We did not limit that research question by U.S. only.

Gregory Brown: Okay.

Nedra Whitehead: We only limited the diagnostic yield.

Gregory Brown: Okay.

Nedra Whitehead: So, the clinical [inaudible] utility studies include both international and U.S. studies.

Gregory Brown: Perfect. Thank you.

Nedra Whitehead: So, this is the one study we found on safety of Hamilton, et al., was a brief study on CMA testing among kids in the British equivalent of foster care. They reported that four of six cases that were tested had abnormal results, and in one of those cases, an application to adopt the child was withdrawn, because the child had a chromosomal abnormality that had been associated with autism, even though the child had absolutely, at two or

three, had absolutely no symptoms of autism. The study was rated as having a very high risk of bias, and under the metric we used to assess risk of evidence, the evidence is limited to observational studies having a maximum rating of low, and we graded this evidence as very low.

Before I move on to diagnostic yield, I want to touch on the earlier discussion about false-positives. There is a paragraph in the discussion of the report, not in the main result section on false-positive. It's based predominantly on one study that was explicitly evaluating SNF based arrays compared to an oleo nucleotide array that was in use in clinical practice at the time. It tested the same patients across all the five different arrays and found false-positives mostly due to the software used to call the array. In some cases they were not recognizing that the same variant was present in the parents, and in some cases, it was misinterpreting the actual array results. Most SNF arrays have evolved since that study was done, but they were, I just wanted to clarify that the false-positive findings there are not... they weren't in use, arrays that were, at that point, in use in clinical practice.

So, the arrays that were in use at that point were being used for research, and they were evaluating them for use in clinical practice.

Gregory Brown: Okay. Thank you.

Nedra Whitehead: Diagnostic yield is the proportion of tested patients for whom chromosomal microarray reveals a pathogenic copy number variant that explains the patient's clinical symptoms, also known as their phenotype. For reference, the diagnostic yield of karyotype in this population is approximately 3%. We included six studies on diagnostic yield of chromosomal microarray. Four were consecutive studies of patients from clinical or laboratory referrals. The indications varied and were often not well specified in the paper. Two studies were patients with specific clinical symptoms or diagnoses. We also included the 2015 Blue Cross/Blue Shield technology assessment.

Five of the research studies examined chromosomal microarray. I'll explain the presentation of the evidence by going through a summary of the Henderson article.

Gregory Brown: So, when I was reviewing this table, just so I'm... sometimes you specify children, sometimes you specify adults, and others you don't specify. So, unspecified is both children and adults? Is that?

Nedra Whitehead: Unspecified usually means they didn't specify it in the paper.

Gregory Brown: Okay.

Nedra Whitehead: So, some studies explicitly stated that they only included children. The [inaudible] study was explicitly in adults and did not include children. The others, we took all the patients that came in and didn't say how many of them were children and how many of them were adults. The annoyance of doing systematic reviews. So, the Henderson study, the sample of this study was all patients for which laboratory had received a request for chromosomal microarray, excluding request for prenatal analysis or tumor samples. They tested 1780 patients and found 227, or 12.7%, had a pathogenic or likely pathogenic duplication or deletion, because the samples consisted of consecutive eligible requests, and the standard methods were used to determine pathogenicity. We rated the risk of bias in the sample as low. As you can see, the diagnostic yield ranged from 7.3% to 14.9% in these studies.

John Bramhall: Not to derail you here, but, so in that Henderson study, there's a laboratory result, which is picked out, the fluorescent intensity is read, the software flags it, and then it's compared to a database of known pathogenic variants, correct?

Nedra Whitehead: Mm-hmm.

John Bramhall: So, so my question really, and it's a little speculative, is that database of known pathogenic variants going to increase over time, or is it fixed now?

Nedra Whitehead: I would imagine that as pathogenicity gets better understood that smaller and smaller levels of deletion, and as technology changes, it will probably still increase over time.

John Bramhall: So, likely, I mean, again, it's speculative, but likely the diagnostic yield would then, perhaps increase over time, as the technology refines itself?

Nedra Whitehead: Right. And you'll see later the Grant et.al review from Blue Cross/Blue Shield found a 1% increase in diagnostic yield for a year, based on the publication...

John Bramhall: Yeah. I saw that.

Nedra Whitehead: ...year of the study.

John Bramhall: Okay. Thank you.

Nedra Whitehead: Uh-huh. And I went... when I went back to look at the reasons for the difference in our diagnostic yield and theirs on average, I found that the diagnostic yield in either U.S. or non-U.S. studies was 5% higher when you looked at studies published in 2012 or later compared to studies published in 2010 or 2011.

Gregory Brown: So, similarly, the people, presumably the geneticists that are seeing these patients and ordering the majority of tests, are getting better at knowing which patients to order tests on. So, if they order tests on a more appropriate subset of patients, you're going to end up with a higher yield also, correct?

Nedra Whitehead: That's also... that would also lead to a higher yield. I suspect much of the increase in diagnostic yield over those years went from variants of unknown significance to variants of known pathogenicity, as opposed to nailing down the patient population.

So, we can go to the meta-analysis of the five studies of diagnostic yield on chromosomal microarray, and our summary diagnostic yield was 8.8% with a 95% confidence interval of 8.4 to 9.3%.

And while several studies evaluated the diagnostic yield by various patient characteristics or for specific indications, the only diagnostic yield among patients with autism spectrum disorder was evaluated by more than one study, and among the three studies they reported on that in this patient... reported on diagnostic yield in this patient population, the summary estimate of diagnostic yield was 5.4%.

We also in the meta included the 2015 Blue Cross/Blue Shield health technology assessment. They included both U.S. and non-U.S. studies published prior to June 24th, 2015. As I said, they found the diagnostic yield increased by 1% per year based on Euro-publication. Among the 21 studies published in 2012 or later, the diagnostic yield among tests conducted for any indication was 19%, and among the four studies that reported on tests conducted specifically for autism spectrum disorder, the diagnostic yield was 12.3%, which is obviously, considerably higher than our summary estimate. I've investigated a few possible explanations for this. The scientific reviewer for the review thought it was because we had included the 2010 and 2011 studies. Certainly, the diagnostic yield is lower for those older studies, but you still get the difference between the U.S. and non-U.S. studies if you go back and you look at the 2010 and 2011. You still get about a 5 percentage point dot higher diagnostic yield among non-U.S. studies. The testing platform, nor the indications, seemed to explain that either. So, it's either that the non-U.S. studies better tailor who comes in

for whom the test is ordered, or they somehow or another call the pathogenic variants differently and end up with a greater number of pathogenic variants. Certainly, the NICE professional guidelines are a little more restrictive, I think, than some of ours. So, that may explain it.

So, to sort of summarize this evidence, we included five studies that included over 14,000 patients. The range of diagnostic yield across the individual studies was 7.3 to 14.9%. All of the studies were observational. We did not identify any serious issues with risk of bias, inconsistency, indirectness, or precision. We had some concerns regarding the variability and the classification, the pathogenic variants. That's just because it sort of evolved over time. We rated the overall body of evidence as low. We found only one study that had evidence on whole exome sequencing. I will leave that one out.

We found seven studies that looked at the impact of chromosomal microarray on clinical management. They were quite varied in design. As I mentioned earlier, we used both U.S. and non-U.S. studies for this research question. Two studies identified recommendations and guidelines for the management of patients with specific copy number variants, then calculated how many cases within databases of anonymized cases would actually have those copy number variants. So, they said, this is a list of copy number variants, but there's actually a professional recommendation for how they're managed, and these are how many of all the cases we have reported in this database that fall within that classification. Five studies examined changes in management after a diagnosis of a pathogenic copy number variant by medical record abstraction or by physician survey to determine how many cases the diagnosis had actually changed the management. These studies varied in how they determined if the variant was pathogenic or not. There was more consistency in how the studies defined management changes. All the studies counted the first five on the list here, and two of the studies also included the lifestyle change... recommendations for lifestyle changes.

The list of evidence here spans two slides. As I did with the diagnostic yield question, I'm going to walk through a couple of studies to illustrate the types of studies and how the data are presented. I'm going to start, again, with the Henderson paper. So, with the diagnostic yield information, what they did was they took the 227 with the pathogenic CNV, and they reviewed medical records to determine whether or not the diagnosis of that CNV had changed the patient's management. Of those, 102 cases had a management change, which is 54.5% of the follow-up and 5.7% of the total tested, and they included the five.

- Seth Schwartz: Can I ask a question about that?
- Nedra Whitehead: Uh-huh.
- Seth Schwartz: We have no way of knowing from a retrospective study that that intervention, the management change, was solely driven by the laboratory result and not by other clinical parameters. Is that correct?
- Nedra Whitehead: What they say they did was look and see whether or not it was noted that they had made that recommendation based on the identified duplication or deletion.
- Seth Schwartz: Only, solely on the basis of the test.
- Nedra Whitehead: They did not say solely, but they did say that was the reason behind the duplication or deletion. Having done a fair amount of medical records abstraction, I would agree it would be very difficult to say whether or not it was solely the cause. I'm surprised they found 54%, but it was noted that it was done for that duplication or deletion, but yeah. A retrospective study with no control group, it's very difficult to say. They did try to limit it to those that it was noted that it was due to the duplication or deletion.
- Gregory Brown: So, you say risk of bias cannot be determined, but I'm hearing your suspicion of risk of bias as high.
- Nedra Whitehead: My suspicion of mis-classification is pretty high, because...
- Gregory Brown: Well, that's a form of bias, correct?
- Nedra Whitehead: Yeah.
- Gregory Brown: Okay.
- Nedra Whitehead: I'm not sure that it's a differential mis-classification. I am not sure that they are more likely to count it as, you know, incorrectly count it as having had management change or more likely not to note a management change when one actually occurred, but I think that there's probably a fair amount of ones that were classified one way that really belonged in the other category. There was not enough detail to really know that well. I will note that the... this is one of the states that only used the first five types of management changes, not the lifestyle recommendations.
- Sheila Rege: Question?

Nedra Whitehead: Uh-huh.

Sheila Rege: Sheila Rege here. The Henderson study was done by the lab, correct?

Nedra Whitehead: Yes.

Sheila Rege: Are most of these studies done by the lab published by the lab group or, I know you say risk of bias being low, but I'm just kind of curious, which ones were labs versus which ones were actually the clinical team looking at how it changed things.

Nedra Whitehead: I, let me look at the like I said here. So, the ones that were done by the lab, like, this one. They were an integrated part. It's an academic medical center. So, they're an integrated part of the institutions, how they can go back and do medical records abstraction. The, let's see which ones I remember, and I think Jennifer may be looking it up for me. Okay. So, I know Coulter is also a lab study. My PowerPoint is not cooperating. I think Hayeems was a clinical cohort study. Ellison was done very differently. It was done like the Riggs study I'll talk about here in a minute. It's one of the database ones.

Gregory Brown: As the number one violator of this concept at asking questions, we're just over halfway through, and we have about five minutes left on our presentation time. So, let's hold our questions to the end or maybe after our break. And, like I said, I apologize for my violating that recommendation.

Nedra Whitehead: Okay. So, Riggs is the other study I'm going to walk through. They used the other approach to this question. They evaluated clinical action ability for a 186 phenotypes that resulted from copy number variants that encompass genes that were targeted by the International Standards for Cytogenetic Assay array consortium, array design. So, the consortium designed its own array, that was available at the time of this study and then were diagnosable by chromosomal microarray, and they found 146 phenotypes that had professional practice guidelines or peer reviewed recommendations for clinical management. They then compared that list of CNVs to the 28,526 cases that are reported of pathogenic CNVs that are reported in the ISCA database and found that 4125 of the cases had a pathogenic or likely pathogenic variant, and of those, 1908, or 46%, had one of the phenotypes that were identified as clinically actionable, which was 6.7% of all the cases that were reported in the database, or all the cases that were reported in the database. So, this study, and the Ellison study, used that methodology, and we rated them as a high risk of bias,

with absolutely no information on what these phenotypes were or how they assessed them.

Overall, the studies found an average patient management change because of the CMA results in 27 to 94% of patients with a pathogenic variant, and 3.6 to 6.7% of all the patients tested. We rated the overall body of evidence as very low, because we had serious concerns about several parameters, including the risk of bias. As I said, we found no evidence on health outcomes.

We found no studies that reported on cost-effectiveness, but we did identify five non U.S. studies, they were all done in Britain or Canada, that reported on cost for additional diagnosis when comparing patients tested with CMA as a first line diagnosis to patients tested with some other testing methodology, usually karyotype. The cost per additional diagnosis is an outcome that represents the incremental cost with CMA compared to testing without CMA per incremental change in diagnostic yield, as depicted by the formula on the slide. A negative cost for additional diagnosis means that testing with CMA identified additional diagnoses at a lower cost than karyotyping and a positive cost means that testing with CMA identified additional diagnoses with an additional cost compared to karyotyping.

Slide summarizing the findings from the five studies. The cost for a patient, the cost for diagnosis, and the cost for additional diagnosis are highly varied across the study. The range of cost per additional diagnosis goes from a savings of nearly \$89,000 to a cost of just over \$12,000 and the variation of cost is driven, predominantly, by the different inputs that went into the study. For example, there's one study here with 114 patients. The cost ranged, per additional diagnosis, varied between \$1300 to over \$12,000 depending on whether you were using the costing from the hospital laboratory or the costing from a commercial genetics laboratory. We rated the strength of the evidence here as very low.

So, in summary, the strength of the evidence for all questions was either rated as low or very low. There was some evidence that patients could suffer discrimination due to test results. We found that CMA testing found a relevant pathogenic or likely pathogenic variant in about 9% of patients, and the test results affected patient management in around 4 to 7% of patients tested. The cost for additional diagnosis varied widely.

The evidence base was limited, as you can tell by the ratings of the strength of evidence. Many of the studies included few methodologic details, making it difficult to assess risk of bias. The studies were heterogeneous

in the clinical presentation of the study subjects. The platform arrays used and the criteria for classifying variants was pathogenic or likely pathogenic. The pathogenic variants identified differ, which contributed to the wide range and estimated impact on management, and the heterogeneity among the cost studies was extreme, and none of the studies were conducted in the U.S. from a social perspective.

Health technology assessment also had limitations. We attempted to offset these when possible, but we only included studies published in English. We used a limited number of databases. We offset that by extensive hand searches. We used a single reviewer to screen titles and abstracts. We only included U.S. studies published in 2009 or greater for diagnostic yield, not systematically assess analytic validity or reproducibility, and we didn't conduct any in-depth analysis of cases, breakpoints, or other information on the variants that were reported in the [inaudible].

Dr. Johnson talked earlier about the practice guidelines endorsing chromosomal microarray. Those are usually endorsed as first tier tasks for children with developmental delay, intellectual disability, genoanomalies, or with dysmorphic features when symptoms are not consistent with a single gene disorder or with a well-documented genetic syndrome. She also touched on the payer coverage.

The centers for Medicare and Medicaid services don't have a national coverage determination for chromosomal microarray, because it's not a testing for a condition that Medicare generally covers. Among private payers, CMA is generally covered as a firstline diagnostic test for developmental delay, intellectual disability, autism spectrum disorders when relevant biochemical and metabolic disease has been ruled out. The clinical presentation is not specific to a genetic syndrome, and the results could impact clinical management. I've pretty much said all that already. So, I will save your time and not say it again.

Gregory Brown: Perfect.

Nedra Whitehead: Questions?

Gregory Brown: Actually, I think we're just past our break. So, I have just about 10:00. So, how about we resume at 10:10.

I think we extended our break a little longer than I suggested, if we can come back to order. Nedra, if you could head back to the podium if you don't mind. Thank you. While you're heading back, we should take a

minute to introduce Dr. Amy Yuen. She is a pediatrician and genetic counselor with MultiCare and has agreed to serve as our expert on this panel. Just a brief explanation, the state had mandated that we have an expert member of our panel for different topics. So, we are having... recruiting those experts on each topic. They are a member of the panel, but they are a non-voting member. So, their role is to help us explain some of the clinical insights, as we discussed before. I guess what I often find is it's the generalizability of some of these research results, because that's always the biggest question is, here's the evidence, but how much does the evidence apply to our decision? So, Dr. Yuen, if you'd like to introduce yourself for just a minute, that'd be great.

Amy Yuen: So, technically, I'm a medical geneticist. So, I am trained and board certified in both pediatrics and medical genetics. I currently work at Mary Bridge Children's Hospital, which is part of the MultiCare system.

Gregory Brown: Thank you for joining us today.

Josh Morse: Can I make just minor comment. So, the clinical expert is not required of the committee, but the committee has recognized over the years that it really appreciates having a clinical expert, and the State last year mandated that if you do have a clinical expert, they need to be a non-voting member. I just wanted to...

Gregory Brown: Thank you for the clarification. Okay. Committee members, if you have questions for our contractor.

Seth Schwartz: This is Seth. I have actually have a question for Dr. Yuen first. I'm struggling a little bit with this concept of clinical management, changes in clinical management associated with the test, because it seems to me that developmental delay, autism are clinical diagnoses rather than genetic diagnoses, and I can understand why we would want to know if there's a genetic cause, but realistically, at this stage, what we want to know is, is that going to change how you manage the disease in that individual patient. They weren't really searching for this, but I certainly don't know the clinical background and haven't seen anything in any of the data presented to us that knowing the underlying genetic malformation associated with the clinical manifestation. I don't understand how that is going to change the actual management of that child in any way. And what we're looking at, the outcomes that they looked at for change in management were things like very vaguely, imaging, surgery, and I can't, I don't know that, I can't see in any way how having developmental delay and a genetic diagnosis is going to have you to recommend surgery. So, that makes no sense to me at all. So, I'm just trying to understand, does

this genetic... having the genetic testing results actually change the way you would manage a child with a clinical diagnosis?

Amy Yuen:

That's a very good question, and the difficulty here in answering it is, this is a very diverse group. So, among the kids who might fall into this group with developmental delays or autism or such, the underlying diagnoses that we find are going to be very heterogeneous. So, depending on what we find, the different impacts will be different. So, occasionally, we might uncover a treatable metabolic disorder. That's always a great thing to find when there's something where we can actually go in and medically treat and help you medically. Sometimes, it's an impact of things to avoid or other things we need to be looking for. So, for example, one of the items on that list that was in one of the earlier presentations with the table. So, they mentioned you got to avoid live vaccines. So, we know, and some kids with developmental delays and autism, if we find a 22q11 deletion, they might have an immune deficiency, and they could become very ill if we gave them a live vaccine. So, that's a point where we might stop something that we normally do for kids, because it would be harmful for that kid. There might potentially be a disorder where we might realize, oh, we've really got to also check their heart. We wouldn't have realized there was an association with a heart issue had we not done the testing. The other place it can help is, it can also kind of stop other testing. When you have an undiagnosed child, there's a feeling of restlessness, of wanting to know, well, what is the cause. If you don't find the cause, other testing continues. For example, in children with developmental delays, depending on how severe it is, they might go onto neurology and then neurology doesn't have a diagnosis, because they haven't had testing. So, they order an MRI. And if it's a young child, they've got to get sedated. So, now the cost is starting to far exceed what the cost of the chromosome array would do. And we're starting to invite other potential morbidities from the sedation, which is generally a safe procedure, but some children could have a bad reaction, and we don't know all the effects of anesthesia long-term in these kids. So, it's really hard to answer the question, because the group is so diverse.

Seth Schwartz:

So, thank you, the first part of your answer, though, suggests a rationale for genetic testing of every kid because of the things you could find that might be interventions that you do, and we're not rationalizing that, because that's a whole different issue. Many of the points that you raised where you would intervene, and this was sort of the question I was asking is, if I were to try to explain this to somebody else and say, well, as a result of the testing, we found this, and then we did that, and that changed the course of their developmental delay or it provided an explanation for genetic counseling of the family for reproductive management. I

understand that. That's a clear thing, but the actual changes that would be driven by this testing alone that impact your management, it seems to be very unclear.

Amy Yuen: So, that's wherein the threshold difference lies. So, if we looked at normal healthy, typically developing children, the chances of finding anything in them is quite low.

Seth Schwartz: How low is that? That's one of the numbers I was trying to...

Amy Yuen: That's a hard question to answer, 'cuz we don't typically test them. So...

Nedra Whitehead: We had one study, a normal population that had testing, and they found 0.7% of the population had a variant that was known to be pathogenic. This was an Estonia Biobank, and when they looked at the responses to questionnaires and clinical records for those folks, most of them had symptoms that were known to be associated with that particular variant. They just hadn't previously been diagnosed. So, the maximum amount, I'd say to answer your question, is 0.7%, but if it had actually gotten the evaluation, then the point in a population without clinical symptoms associated with that variant is lower than 0.7%.

Gregory Brown: And just to clarify, that's any pathologic genetic finding, not specified for developmental delay, intellectual disability?

Nedra Whitehead: That's any copy number variant.

Gregory Brown: Alright. So...

Nedra Whitehead: It's not, yeah.

Gregory Brown: ...cancer, anything?

Nedra Whitehead: Uh, right, but it's not a single gene disorder. That wasn't... they weren't including single gene disorders in there. It was specifically variants that were picked up by chromosomal microarray.

Gregory Brown: I think I have a similar question, and maybe I can ask it differently, as we, you know, look at the human genome and we're able to find it and now can do it in individuals, we find these genetic differences, and even if we find that something can be pathologic, my understanding is that the impact on the actual incidence of whatever that pathology may be, the genetic component is very small. It's still more environment, development, all sorts of other things that affect a phenotypic pathologic presentation than

the gene, and that the, like, the deletion that we talked about earlier of almost 100% have colon cancer, but that's rare. It's not the usual. Is that correct?

Amy Yuen: Yeah. So, depending on what symptom or medical issue you're talking about, sometimes environmental impact could be greater, so colon cancer or breast cancer. More of those are not genetic than are genetic related, but for the individual who has a genetic predisposition, the management and the issues are quite different.

Seth Schwartz: As kind of a follow-up question as to how this is actually being currently used in clinical practice, there's... we're hearing some variation here. So, it seems like there is the group of kids who are clinically suspected of having autism or developmental delay or whatever it is. And in that group, it seems like this testing is used to try and nail the underlying diagnosis, and that might guide whether there's additional testing, because there are things that are noted to be associated with those phenotypes. Then, there's this other group of kids who don't have those things and maybe are walking a little bit slowly or speaking a little bit slowly or whatever. We're now seeing some of those kids are being tested to try and put them into a different category? Does that jive with what's actually happening in clinical practice?

Amy Yuen: We would need to assess where are they in that range of normal? Are they just a little bit off the average, or are they significantly behind where we expect? So, there's a lot of thought and evaluation that should go into each of those patients in deciding whether they should get testing.

Seth Schwartz: And is that something that could be operationalized? I mean, I think what I'm... maybe I'm taking a step ahead, but thinking about what our actual task is here, and I'm starting to formulate a concept where we could understand how, in kids who have developmental delay, and the underlying reason is not known how this could be a beneficial thing to nail down the diagnosis and then you know what therapeutic pathways that child is going to go through, but I think the concern is, this wider group of the entire U.S. population of children who could be screened for this. So, there's... you could say totally asymptomatic kids to developmental delay. And then, there's this wide continuum between there. Can you operationalize ... would it be operationalizable to sort of pull out a group of kids in that segment who may benefit from this technology or not, 'cuz I didn't really see that at all in any of the data that was presented to us.

Gregory Brown: Actually, can I interrupt for just a second. Poor Nedra is standing at the podium for this whole discussion and not being... and that's fine. So, I

guess my question is, is do we have questions for her? And if we do, let's ask her. And if not, let's let her sit down, and then we can have our committee discussion.

Chris Hearne: So, on your slide 47, the conclusion slide, since we heard earlier that people are already thinking about using this data in other places in this analysis?

Nedra Whitehead: Yeah. I will say, I don't know what data they used. They did not use this report.

Chris Hearne: Okay.

Nedra Whitehead: Because it wasn't out for anybody to use. So, I don't know what they used. It was not this... it was not our report.

Chris Hearne: But it will be in the future available?

Nedra Whitehead: Yeah. It is now posted, so.

Chris Hearne: Right. So, under your chromosomal microarray results prompt, prompt is the operative question there. Is it associated with management changes, because if they're retrospective, you can't infer causality, right? That's kind of fundamental. So, is it truly... can we say on the basis of the data evaluation that we've done that there is maybe a prompt? Or is it more accurate to say that it's associated?

Nedra Whitehead: So, I will say that the notes in the records for the medical records abstraction or the response to the surveys, the physician said that they were prompted by the chromosomal microarray results. Beyond that, I can't say. I agree that you can't prove that. It's not like an epi association study, you know? If I say I went yesterday to catch a plane to Seattle to come for this meeting, I went yesterday to catch a plane for Seattle to come to this meeting. The intention behind that is different than trying to associate an environment cause and its association, but I can't... you can't prove...

Chris Hearne: You would stand behind prompt, the term...

Nedra Whitehead: I would stand...

Chris Hearne: ...prompt?

Nedra Whitehead: ...behind prompt.

Chris Hearne: Okay. Thank you.

Nedra Whitehead: I will stand behind that, at least, the studies were designed such to look specifically for management changes prompted by the management changes, and that they designed their questions and their abstractions so that they got the best result of that that they... the closest to that that they could get, given the practicality of the study design.

Chris Hearne: So, then, so the second bullet point under that finding on very low strength of evidence, the finding is not their pathologic findings prompted a change in management, because you're standing behind that. The low evidence is...

Nedra Whitehead: The low evidence implies... so the findings there say that this is what these seven studies showed.

Chris Hearne: Right.

Nedra Whitehead: The low [inaudible] that if you did another seven studies, it might change. That the [inaudible].

Chris Hearne: But the fact that it prompted a change in management might be quite different.

Nedra Whitehead: Right. And more specifically, I would say, the number, the proportion of kids for which there was a change in management might change. I would be very surprised to find that it went to zero, but it might... but that proportion may very well not help if you had more studies.

Seth Schwartz: On the cost-effectiveness summary, slide 39, I wonder if you can just help me to understand this number a little bit better. So, it says it could be cost savings of up to \$88,000 per diagnosis. Is that suggesting that using this testing would avoid so much other stuff that it could potentially save that \$90,000?

Nedra Whitehead: That's how they got to that number.

Seth Schwartz: Okay.

Nedra Whitehead: The additional testing that might be avoided, additional visits to specialists, those kind of things are what went into the number.

Seth Schwartz: Okay. 'Cuz that's a fairly huge number. Maybe you can help us understand a little bit what could potentially cost \$90,000 to manage one of these children without genetic testing. Is there?

Nedra Whitehead: That requires a little more cost about... the cost of other procedures than I have. Leila is on the phone. She did this analysis. She might know. I don't know the current cost of an MRI, but I will agree that it's a not uncommon follow-up for kids with intellectual disability or autism, but some of the type...

Laila: This is Laila. Can you hear me?

Nedra Whitehead: Yes.

Laila: Yeah. So, that number is not... it's the cost... additional cost per additional diagnosis. So, you can't really think of it as the episodic cost for one individual. So, what they do in the study is they look across the entire study population and they calculate the cost with first lines they may use. They compare it to the cost in CMA used not at all. So, karyotype predominantly. And then they look at the difference in diagnostic yield to come up with that number. So, it's not really an episodic cost, say of one case and how much they would save if they got CMA testing if that makes sense.

Gregory Brown: So, if I understand correctly, you're saying if you did testing of karyotype testing versus the CMA, say you tested 100 people at \$1000 a piece and found one diagnosis, that's costing you \$100,000 for the one diagnosis whereas if you did the CMA and tested 50 people or whatever and found five, that's \$10,000 per diagnosis and the difference is \$90,000 between the two?

Laila: That was a little hard for me to follow in my head, but yeah. It's not the cost of sort of per diagnosis. Really, the incremental cost for the additional yield and diagnosis.

Gregory Brown: Okay.

Seth Schwartz: And just to clarify, compared to what? So, is this compared to standard diagnosis for developmental delay, compared to other genetic testing?

Laila: Yes. Compared to standard diagnosis, which typically involves karyotypes, but it varies quite a bit across the studies, which is probably why the estimates from the different studies are so widely varying, because what they actually put into their cost inputs was highly variable.

Seth Schwartz: Okay. Thank you.

John Bramhall: Dr. Whitehead, in your slide 50, which is simply a list of payer coverage decisions, do you happen to know... so, the listing here shows quite a lot of coverage is already in place by commercial entities, covered for specific indications. Do you happen to know whether the indications include some restriction on who it is that can define those indications? In other words, it's addressing this question of where the test ordering should be filtered in some way or is being filtered in some way, as to who it is that can order this test.

Nedra Whitehead: So, my memory is that it is...

Josh Morse: Nedra, could you please use the microphone, please?

Nedra Whitehead: ...yes. Sorry. So, my memory is not that they restricted who can order the test, but they restricted on sort of what other things had been tested for and what the kid's symptoms were. Laila, do you have any other memory?

Laila: Yeah. I believe there was one policy that required only a certain kind of professional who didn't work for a commercial lab could order it. I'm looking in the final report to see if I can pick it out quickly, but it wasn't... it certainly wasn't universal across all the testing, but I think one or possibly two may have specified who could order.

Nedra Whitehead: Dr. Johnson says it was the CIGNA policy.

Gregory Brown: I thought it was CIGNA.

John Bramhall: Alright. And so Amy, just as a follow-up, the... we see it in a couple of locations, this idea that the testing would be a first line, first response to presumptive diagnosis, and yet, I think you sort of suggested in your earlier statements in clinical practice, there's a big workup going on coincidentally, and this genetic testing is after a certain amount of intellectual input and study. In other words, it's restrained in some way. It's, it's not the first line of attack at the moment. Is that true?

Amy Yuen: You want to look at it... technically, the first line is the history, physical, family tree. You're going through all of this detail to see if there's anything that matches clinically before you even start ordering a test. And then, also determining do we need a test.

- John Bramhall: And do you think it's the kind of test currently that would be, a child goes to the well, annual well child checkup and a pediatrician examines the child, has a suspicion that there might be an intellectual impairment or a spectrum disorder. Is it that person that then would be thinking of, let's run a test and just see? Or is there a lot of work that you would expect to be done before the test?
- Amy Yuen: Initially, depending on, let's say this is a pediatrician and kind of how well they have known this child. How long have they been following the child, and how comfortable they feel with ordering the test versus referring the child for additional input?
- John Bramhall: And would you advise us to take steps to put organizational constraints on testing if we were to go that direction?
- Amy Yuen: I don't think we have the capacity in Washington State to...
- John Bramhall: Physical capacity?
- Amy Yuen: ...the physical capacity to put the restraints.
- John Bramhall: Okay. Alright.
- Amy Yuen: One other point I want to make when we're talking about this is, first line, part of this is in reference to array versus karyotype. Some of the report and guidelines are looking at this as do we do a karyotype first, or do we do an array first? And as the use of arrays has progressed and we have better and better array technology over the past ten years, the thought is, well maybe it's now actually more cost-effective to not do a karyotype first and then get an array but to instead just go to an array. Where I am now, they're both approximately the same price would get billed out. So, it's more efficient, if I suspect a chromosome disorder, to order the array, because I'm more likely to pick up the small deletions and duplications that you won't be able to see doing karyotype.
- Sheila Rege: I'm sorry. Not a question for you but for the expert. So, I was thinking of, with the multiple congenital anomalies, to kind of consider adding something like nonspecific to a well-delineated genetic syndrome, but maybe that speaks to your karyotype being the same price now. So...
- Amy Yuen: Yeah.
- Sheila Rege: ...maybe that's not.

- Amy Yuen: Sometimes, I might see a child and easily recognize a syndrome, but with the current pricing, it actually starts to become more advantageous just to do the array. So, we had a patient who came to clinic. I'll just give you this as an example from this week, and he appears to have Cri du chat syndrome. If I do the array, the price is very close. It's within less than \$100 difference. The array will tell me the exact size of his deletion, the laboratory will do a free follow-up FISH that they won't charge me for. And if I need to test the parents with the current arrangement I have, they will include that part for free. So, it becomes cheaper to just order an array for this little guy, even though he appears to match up with the syndrome.
- Sheila Rege: So, two questions, and I had one. How do you prevent somebody from... if they order an array a first line then add a karyotype later. I mean, is that something we can?
- Amy Yuen: Well, there are ways...
- Sheila Rege: Specify?
- Amy Yuen: We're actually looking at this in our hospital system. So, we have added a little tool in the EMR when they go to order a karyotype, we called it the karyotype versus array decision tool. And it asks them a couple easy questions. We have to make it not too long, because if it's too long, people will click on it and say, ugh, I'm overwhelmed, and I don't know all this stuff. So, we picked a few key questions that would help you decide whether the array would be better or whether the karyotype would be better. So, we had some simple questions. For example, if they suspected Down syndrome, it's better just to go ahead and get that karyotype. If they had some family history that made them concerned about what they call a balance translocation where it's starting to look at the structure of the chromosome being important versus just is there a missing or extra piece. Then, it's more useful to do the karyotype. So, we put a few little questions so that the provider could go through click, click, click and see, okay. Which one would be more cost-effective for this patient to start with?
- Sheila Rege: And the second question is related to FISH use. In your practice, you were able to negotiate something so there was no extra charge for FISH, but it may be an extra charge in some labs. So, for the agency, how do you do that? I mean, because that's... FISH is expensive, at least in cancer.
- Amy Yuen: I think this is an enormous challenge, because when you're approving a test, you don't know how much it's actually going to cost for that specific situation. It could vary depending on where the test is being sent to, which institution is ordering it. I think that's an enormous challenge.

- Female: I have a question about where this test is being sent to. Dr. Johnson mentioned that the costs coming in were 1 to \$7000. So, my question is, are different labs providing different quality results, or better... is a \$7000 test somehow better than the \$1000, or is there just a much greater markup? And then, a procedural question, can we intervene there? Can we grant this test up to a certain point, limit the amount of money that we'll pay for this type of testing?
- Amy Yuen: Most of the labs are using very similar platforms. You're going to get similar quality against a number of different labs. The number of labs that are running array tests is increasing. They have differences in pricing because they're all different business entities. So, they will charge different amounts, and they may give discounts to some hospitals depending on volume. Some places may be able to do internally. For example, Seattle Children's Hospital has a lab, and they can run the arrays in house. So, they don't have to deal with other parties marking up the price for them. Also, again, this is a challenge.
- Gregory Brown: Any more questions for Nedra? Thank you very much.
- Nedra Whitehead: Thank you.
- Gregory Brown: Then, continue our discussion on, just among the committee. Any other questions for our expert? Do we want to start discussing thoughts and maybe where we're leaning?
- Female: I didn't get an answer to the second half of my question, which is, is this an all or nothing? We pay for it and we'll pay whatever cost the lab bills, or is there a second tier sort of, we'll pay up to a certain cost?
- Josh Morse: Typically, the clinical committee does not look to set a price, though you have historically looked at, when you had solid cost-effectiveness data to say, there's a return at this level of reimbursement, but there's not beyond this. That has occurred.
- Female: So, if we approve this and everyone shoots their prices up to \$7000 per, we don't have much say in that?
- Gregory Brown: Well, again, that's up to the State and the Health Care Authority to negotiate that, is my understanding, not... we determine coverage and the State determines the pricing. Okay. Perfect. Thank you.

- Sheila Rege: If we look back on and kind of to give us some guidelines, I understand that we don't have enough genetic counselors and specialists, is there anything else we can put in the language that, and I'm thinking things like, delineated genetic syndromes or non-syndromic, or something that would help tighten it, so it'd be... so this test is ordered for the appropriate patient and not a little willy-nilly? Because, I mean, family practice doctors or pediatricians are stressed and mom comes, just, I want this test. It's, it's easy to say, well I can't do it because here's in the guideline. So, are there any recommendations you would make as an expert?
- Amy Yuen: That's a very tough question. I think the committee has already kind of worked toward making a list of certain features that you need to have one of these, the autism spectrum, the multiple congenital anomalies, developmental delay. I'm hard-pressed to think of what else to add.
- Gregory Brown: I will add my response to that. And that is, I think this committee helps those pediatricians and says these are the State guidelines for ordering these tests. I will tell you that I certainly use the State guidelines for opioid prescription when I have patients with joint pain coming and requesting pain medications. And I can tell them, I'm a surgeon. I'm only supposed to prescribe pain medications for a certain postoperative period. So, if it's before surgery that needs to come from your primary care provider. So, I like the State guidelines. They're much clearer. They're much easier to follow. So, I think that's the role of us as the committee to help clarify things for the providers.
- Sheila Rege: Should we add that if this is ordered then really karyotype testing, in addition, is not generally recommended, or should go to a peer review? Would you, would you recommend anything like that based on your practice?
- Amy Yuen: In some cases, a karyotype might be the better first test. So, we wouldn't want to restrict that.
- Sheila Rege: But not after, after you've ordered a CMA.
- Amy Yuen: Usually not. There are rare exceptions where you might need to, depending on the imbalance found, you might want to look for structural rearrangements. It's not very common for us to order a karyotype after an array.
- Sheila Rege: I'm wondering if there's some language that could be inserted that it's not common, in addition to this, and I don't know the mechanism to do that.

Gregory Brown: Well, yeah. I think, I think we're getting further down the discussion with that.

Chris Hearne: I had a follow-up question about the coverage, the other that commercial payers have provided. Do we know anything about the history of their coverage decisions? In other words, did they have pretty open coverage and then start to put restrictions on, because they saw what we are all fearing, which is an explosion in the utilization of this, the same trajectory that has already been shown, both financially and in terms of volume? Is that what has been seen nationally, and have they changed their coverage? Do you know?

Amy Yuen: In fact, some of the commercial providers were denying it as investigational, and some of them have now moved to covering it. So, I've also seen an increase in some of the commercial providers covering it.

Chris Hearne: This specific indication?

Amy Yuen: Specific.

Chris Hearne: So, they put, when they... when they added the coverage decision, they put the indications in? It's not that they...

Amy Yuen: That appears to be the trend.

Chris Hearne: ...subsequently added restrictions on it.

Amy Yuen: It feels like they came together.

Gregory Brown: So, I have two, well, one is a clarification and if I heard right from two of our public comment speakers, that they didn't feel that there was capacity for all of these children to be referred to a geneticist, but there was capacity for some sort of utilization review without having to see the patient. I'm seeing two people shake their heads, so. Thank you.

Amy Yuen: Well, the clinical laboratories can be very helpful, because they see the test order coming in. Where I am, the laboratories will call us if there's something that seems unusual. So, an example I was sharing with someone else, there was an order for an array, a karyotype, and a FISH all at once. So, clearly, we did not need to do all three of those. So, we were able to reach out to the community provider and say, okay. Clearly, you're very worried about this child. What's going on, and help kind of guide. Okay. Where do we start with this workup? So, a laboratory could be a very valuable in kind of bridging that unmet need.

Gregory Brown: Okay. And my second question has to do with the safety issue, and it's more general. Previous discussions on IRBs, there was always a question of genetic testing, that it exposed those patients to discrimination for preexisting conditions with insurance carriers. That theoretically went away with the Affordable Care Act, and if that's repealed, potentially insurance companies could readdress preexisting conditions. So, would that be a potential safety issue if patients had incidental findings of other health conditions that they were then discriminated against?

Amy Yuen: This is a question that does come up. Some families even ask the question. They've really thought about it. One of the issues that goes with this is not just your health insurance, but your life insurance, disability insurance. You could be denied life insurance based on some of these findings. So, this is particularly important when we've had a finding. So, the child has come to us with symptoms. So, obviously, it is not as much of an issue with a child, but sometimes we might find something, then we start thinking about other family members who might not have any symptoms and we do kind of start to address, okay. This particular issue might cause you problems with life insurance. Do you already have life insurance? What are your plans? What are your thoughts? What would you rather do? Know that this is a risk. So, for example, if there was a child that found the gene mutation that led to colon cancer and we start talking about well, was this brand new in the child or did they inherit it from a family member? Are there other family members at risk for colon cancer? This could make this extremely hard for you to get life insurance if this is known. What do you want to do? So, it does play in a little bit.

Gregory Brown: Thank you.

John Bramhall: I just want a clarification, which I think I have straight in my head. When I was reviewing this information earlier on, in particular with reference to autism and the spectrum disorders, I actually thought that an objective test, provided they came back 'positive' would be useful in the interest of the State regarding this whole controversy about vaccination and autism. So, and I don't want, and I don't want to go into that, but I was thinking, okay. You've got worried parents with a child that's showing signs of autism and the concern that they have, rational, irrational, whichever, is that the vaccination is the trigger and it feeds into a whole lot of debate there. And then, my ears picked up when you mentioned that same linkage, but am I right? You were mentioning it in a slightly different way. You do a genetic test, the genetic test comes back with information about a variant, and you, in part of your testing, you were describing that variant

could be a susceptibility to vaccination, but from the context of an immune disorder.

Amy Yuen: Immune disorder, definitely.

John Bramhall: I have that correct? And that test would not be...

Amy Yuen: Not in autism.

John Bramhall: ...it wouldn't have been taken without the child already showing signs that were worrisome? Is that...

Amy Yuen: Exactly.

John Bramhall: ...my understanding is good? Okay. And I do think that it's not compelling, but I do think that if you can objectify in a word some of the diseases that people have for a variety of reasons concerns about in relationship to environmental issues, and previous medical treatment. I think that is an additional benefit to society, in general, in my opinion. So, thank you.

Amy Yuen: I agree. Some families, once they've had a diagnosis of autism, they become fearful, and they might not vaccinate the rest of their children if they don't know what caused the autism, but if they can find the underlying cause of the autism and understand no, your child has a genetic abnormality that predisposes, and it was not related to his vaccines, that could provide some reassurance. And the other healthy siblings could hopefully then go get vaccinated.

Josh Morse: Dr. Walsh is listening on the phone, and he asks that if people could please state their name before they speak, it would be helpful to him. Thank you.

Gregory Brown: Okay. I'm not seeing anybody looking to ask questions. Do we want a discussion for a few minutes, thoughts? Do we want to kind of use our tool? Are we far enough along in our thought process? Okay. Let's go to our tool, looking at safety outcomes, if I've remembered the report, other than phlebotomy risks from getting a specimen, the safety issues that they raised were around adoption and discrimination. There's just a brief discussion about discrimination in terms of getting future life insurance, disability insurance, potentially health insurance. Any other safety issues that others are thinking about?

Seth Schwartz: I don't know that it's directly... this is Seth. I don't know that it's directly a safety concern, but I think this concern of need for additional testing based

on incidental findings. Again, I'm not sure if that's necessarily a safety concern.

Gregory Brown: Well, I mean, certainly, yeah. I think there's... I mean, that's a fundamental issue around all sorts of tests, the risk of the workup of a false-positive outweigh the benefits.

Chris Hearne: The point about the insurability, and the risk mitigation, that is a huge potential issue. And it's not what in front of mind of either the family and certainly not the child at the time the testing is done. And if it's ordered by a non-genetic professional, like a pediatrician doing a well family check or a family practice doctor, they may not counsel, probably won't. I mean, it just, in the timeframe that they have for that, you just can't see that happening, that the risk of doing this and finding out something, because once you know it, you know it, and on insurance forms, school, etc. forms, you will be asked do you have any preexisting conditions. So, this is a lifelong issue. I see some of our community people nodding. I mean, I think that that is a huge risk.

Amy Yuen: One thing that will help mitigate that is, hopefully in this situation, we're looking at the pediatricians testing a child who already has symptoms. So, that's already documented in the record. And if it becomes relevant to also test the parents, hopefully at that stage, they've referred them out to someone else, because of the abnormal result finding on the array. So, that's one thing that will help there. Another point I would add to your earlier comment is emotional distress on an unexpected secondary finding is also an important thing to keep in mind. If they're bringing the child in for developmental delays, and we have the secondary finding of the colon cancer gene, they weren't in the mind frame of thinking that that might be a possibility. So, there's also risk for some significant emotional distress or fear.

Carson Odegard: Carson Odegard. There is also, once you find these incidental findings and if proper follow-up wasn't performed, there's a risk there, as well, a safety risk. I mean, there are a certain amount of patients that would go beyond the testing realm, taken to the nth degree, and then there's others that would just say, no. I don't want any more information on this at all. I, I'm done. And then you've got a safety issue, I'm concerned with that.

Mika Sinanan: First time, I've used my, sorry. The point you raise about symptoms, that is... a symptom is a variant of normal to a clinician. So, the family comes in and has complaints. So and so is not like their brother and their sister. They have, there's something different about them. So, I think that symptom issue is a very slippery slope. It's not as clear that clearly

somebody has symptoms or is normal. It's a very big grey zone that I think John was talking about earlier. This probably gets to some of Sheila's points, as to how do we narrow the focus, try to narrow the focus in terms of the, the restrictions. There are some suggestions, and I think the indications, or the guidance towards approval or support for this by payers have tried to address that, but really, the test is what's going to happen or is this going to open floodgates for a lot of symptoms.

Gregory Brown: So, I think I'll say this is a scope issue to me. So, we've run into this in the past. We can't come up with our own definitions of developmental delay, autism spectrum disorder, or you know, multiple congenital abnormalities. So, we can specify the conditions. Clearly, the medical community has definitions for those, and it would be the agency's implementation of how to say that yes, this qualifies. They meet the diagnoses or whatever, based on whatever definitions they want to come up with. So, I think, we can say these are the conditions that we think it's appropriate, but we're not gonna be able to say these are how we're going to define each of these diagnoses. I think that's consistent with what we've done in the past.

Mika Sinanan: I agree.

Gregory Brown: Yep. Okay.

Kevin Walsh: This is Kevin Walsh. Can we, I feel like this discussion is catapulting way ahead. I thought we were discussing safety, and now we're talking about operationalizing a decision, which we have not made yet. I would like us to limit the discussion right now to safety question before us.

Gregory Brown: Kevin, I agree. And I, I think we reigned back in. Any other safety issues or Kevin, did you have any comments?

Kevin Walsh: I share the same concerns about unanticipated consequences, both for life insurance, but the case of the parents who decided not to adopt a foster child because of a chromosomal anomaly that was found when the study was done, is huge. So, I think there are a lot of safety issues here that are not maybe right in front of our nose, but are lurking.

Amy Yuen: This is Dr. Yuen again. The other side to that case report of the child where they decided not to adopt, I would also like to think of it as we want there to be a good fit between the adoptee and the adoptive family. If they don't feel comfortable adopting that child, are they at risk for abuse, neglect, or I've seen a child who was adopted and got returned, the emotional impact on him was devastating. So, we want to make sure they have a good fit first. So, if the family wasn't comfortable, I don't... this is different than

someone just applying for a job. This is a family fit where they're going to take this child, care for him for life, be bonded in ways that are just hard to really quantify. So, I don't know that we can necessarily look at that one reported incident as a global reason to not proceed.

Sheila Rege: This is Sheila Rege, but I think... I understand the genetic counseling is in short supply, but some, for safety reasons, I think encouragement of referral, for explanation of the genetic disease, possible outcomes, risks, inheritability, I think would be important to alleviate that safety concern.

Gregory Brown: So, again, I think we're... in respect to Kevin's earlier comment, I agree. I think, to me, that question is moving us to efficacy and diagnostic yield. So, we want to make sure, anybody have any other comments on safety, and we can move to the next one? So, efficacy, effectiveness outcomes. So, we have diagnostic yield, earlier diagnosis, change in management, what's not missing is health outcomes, which the answer was no health outcomes in either the U.S. or non U.S. studies whatsoever. So, we have no evidence on health outcomes, to me, which is a big unfortunately. I think if I may reinterpret your question about referring for counseling, I guess what I would say is, there's not a capacity for everybody that gets a CMA ordered to see someone, but certainly, my guess is that virtually everybody that comes back with a positive CMA would get referred. Is that correct?

Amy Yuen: Yes. We try to work with our clinic flow to make sure that when there are patients out there who have had an abnormal result that they can get referred and they're not waiting long amounts of time with parents in distress over what is the meaning of the result. So, I believe there is very good capacity to take care of that in our state.

Kevin Walsh: I'd like to address efficacy. As a primary care provider, my understanding is that this is a clinical diagnosis, developmental delay, autism spectrum disorder, I mean, I do screening for children at well child checks for these. So, the test is not going to help us make the diagnosis. I'd also like to add that these problems, there's no definitive therapy. So, we're talk... my understanding of this literature review is that we have a lot of ancillary... potential ancillary benefits, but no primary benefits. I'd like to understand if other people are seeing it differently or am I on track?

Gregory Brown: So, if I can hear what you're saying, Kevin, this is Greg. So, in other words, if there's an intellectual developmental problem, there's no specific treatment that's going to fix some genetic abnormality, but by ancillary, you mean, they may get additional classes or teaching within the school system?

Kevin Walsh: No.

Gregory Brown: Things...

Kevin Walsh: No. The genetic testing isn't going to... that's all, I think, Greg, that's all based on the clinical evaluation of the provider of the family of the school. I'm talking about finding out that this child has an extremely rare cardiac condition that might not have been discovered otherwise. Or is it risk of colon cancer, the examples that the geneticist who is our expert posed. What I'm saying is, those are ancillary incidental peripheral benefits to this testing. In terms of the question of does it further the care of children with autism or developmental delay, I don't see any evidence that it does that.

Laurie Mischley: In response to that, I'll just say I think that there is a difference between ancillary potential... I see that as prevention. I think our job, as physicians, is also to practice prevention, and if a patient is experiencing... coming to you presenting with atypical symptoms and perhaps congenital anomalies and... I don't think it's unreasonable to test and screen for things that may prevent a colon cancer diagnosis later on or heart issues later on. So, I just want to champion prevention as part of our job as clinicians.

Kevin Walsh: I respect prevention, but that's not... again, that's not the question for us. Unless I'm misinterpreting the question, the question is, in terms of the treatment of children with developmental delay and autism spectrum disorder, does this testing further their... does this testing improve their car? And your question really... you go back to, is there evidence that we should do genetic screening on everybody who walks in the door, because the benefit you posed is applicable to every patient I see, not just these.

Laurie Mischley: This is Laurie again. I would just frame it a little differently in that perhaps the developmental delay is the first of several manifestations of an underlying genetic disorder.

Amy Yuen: Dr. Yuen again. It also depends on what we find on the testing. We have some genetic disorders that are treatable, and I think the number is going to be increasing. Right now, these are mainly metabolic disorders, but I am seeing an increase in more enzyme replacement therapies, medications that can be given. Sometimes, these initially present with a developmental delay or some kind of less specific manifestation that wouldn't lead you to pick out that exact metabolic disorder, but if you find it earlier, you can start the treatment, and they tend to do, in general, with different metabolic disorders, they do better.

Seth Schwartz: So, this is Seth, and I kind of agree with what Kevin was saying. I'm sort of struggling to figure out how this testing is used and why. I think... and that's... and in that, I'm trying to understand what our task really is here, because there's a couple different possibilities here. Yes, knowing more about people's genetics and all the things that happened to be may be great and maybe even greater over time, as we know more how to treat some of the things we may find, but for this particular test, are we talking about... is this test useful for improving the management of children with Down syndrome and autism. If that's the question, then that's a very focused question, but I think that's... my understanding is, this is a broader view about this testing in general, and I'm still having a hard time wrapping my head around why we're actually ordering this testing, because I agree with what Kevin said in that if we're ordering this testing to help make the diagnosis of autism or of Down syndrome or of whatever, then I'm not sure we saw any evidence that it's going to be any better than the clinical ability to do it. Maybe it's cheaper than the current way. Maybe it's not. That's just kind of vague, but in terms of whether it's improving the management of these kids, we didn't really see anything to that... any evidence to that light either. So, I'm just still trying to figure out how this testing is useful. We can kind of speculate in a lot of ways that it might be useful, but I'm not saying... I don't think I've seen a lot of evidence to that fact.

Tony Yen: This is Tony. I think the literature that we have in front of us over here shows that there are changes in management. Whether or not those changes in management are correlated with any health outcomes is still very unclear, I think. That's the bottom line, but it seems like, at least my interpretation of the literature so far, is that there are changes in management for patients that actually come back with positive CMA screening is what I see. I don't think this is really involved in making diagnoses, in terms of autism spectrum disorder or other, say, congenital abnormalities, necessarily, maybe. Please correct me if I'm wrong, but I'm compelled in that it seems that there are changes in management and for those that have chromosomal abnormalities, that's a pretty high percentage. I don't know what the efficacy of those changes in management really lead to, though. That's where I... it's kind of a black hole for me.

John Bramhall: This is John. Can I just ask you as a follow-up, is something like a glycogen storage disease problem, is it likely now to be picked up first from, like, a CMA screen or are those things, PKU and all the things that we know about, are they picked up in totally different ways and wouldn't be influencing a desire to run a CMA test.

- Amy Yuen: Certain metabolic disorders would not be well picked up by an array. Some of them are screened for on the newborn screen, and we're looking for kids very early on. They're all treatable disorders that are on the newborn screen. Now, among other metabolic disorders that are not on the newborn screen, some of them are more commonly related to point mutations, some have deletions that can occur, as part of the alteration in the gene. So, it depends on the specific disorder, as to how well the chromosome array would pick it up.
- John Bramhall: But it is true, probably, to say that a CMA result... it's not unreasonable to think that in a proportion of cases there is an intervention that then will be restorative in some way. It's not an incidental. It's not the colon cancer issue. It's we have found a genetic change through CMA that we think is associated with your presenting symptom, intellectual developmental delay, whatever, and here's what the lifestyle change or the dietary change or the medication change is suggested to help cure or treat the problem, which you presented with. Is that, that's an unreasonable situation to describe or one that's very reasonable?
- Amy Yuen: No. That can happen. For example, in cystinosis, one of the common mutations is a deletion that you can pick up on a chromosome array. This is a disorder that leads to renal failure in children typically if untreated die by the age of 10. There is a relatively inexpensive medication they can take that helps with this. If they are diagnosed early, we can prevent renal failure and hopefully have a long life.
- Carson Odegard: This is Carson. So, when we looked at that slide 19 on the left hand column, is that all-inclusive? I mean, so the cancer screen is part of the screen that... it's part of the array. So, when we talk about some of these other conditions, is that what it's looking at or are there other things that aren't on this list?
- Amy Yuen: Dr. Yuen again. I think this is just a list of examples of ones that were found by this report. So, this would just be example set, not necessarily everything that you could potentially pick up.
- Carson Odegard: That's what I'm wondering, because not seeing the lab report and seeing all the different things that could possibly be on that list, I'm just finding these things alone can open up a lot of additional testing in itself. So, that's just what they found in the report. Okay.
- Amy Yuen: Yes. I would expect this is just the example of what they happened to find in this particular group.

Carson Odegard: Alright. Thank you.

Mika Sinanan: Can I ask you, Mika Sinanan, can I ask you for a hypothetical. Assuming that you had a child who was covered by Medicaid, and this was not a covered laboratory test, genetic test, what would you do?

Amy Yuen: Depending on how severe the symptoms are, occasionally we ask the hospital to absorb the cost. So, if we feel this child has severe symptoms, it's very important to do this test. We have no way to pay for it. Well, let the laboratory know that ethically, we feel we need to proceed with testing. We don't have coverage, and the hospital is going to absorb the cost. There's a limit to the number that the hospital can absorb before they go out of business. So, we can't test everyone that comes to mind. So, we have to think, if I'm looking at you, and I'm going home and feeling disturbed that I have this extremely symptomatic child in front of me and I recommended a test, and it's not getting covered, and I feel ethically that this is a bad situation, I ask the hospital, I'll say we have this child. She is severely delayed. She is having intractable seizures. We're trying to figure out what is going on with her so we can guide management. The neurologist is trying to figure out, how do I treat these seizures. I need to do some testing. Then we just absorb it through the hospital.

Mika Sinanan: So, thank you. That speaks to the efficacy question in my mind that you feel strongly enough that you will take further steps, as a professional in the field, to intervene and make sure the testing is done, because there are management issues, or management decisions, that would come from that that you feel would clearly change the pathway, direct management, significantly differently, as opposed to, well, we weren't going to find anything that would change what we would do. So, let's do something else, or we're going to recommend education and antiseizure medication, and do an MRI scan, because we were going to do those anyway. I mean, those are sort of two polar opposites, but you were saying you were advocated?

Amy Yuen: Yes.

Kevin Walsh: This is Kevin Walsh. I'd like to just point out something about the example that was just given. So, this was not a child who presented with developmental delay. She described a child with intractable seizures. So, even if this... even if our decision regarding using CMA for developmental delay and ASD would prevent coverage, this is a diagnosis of intractable seizures. So, the testing would be covered. So, I don't feel that was a fair example.

Amy Yuen: In the example, the child is also severely delayed, and epilepsy and seizures is not on the list of criteria that I'm seeing if I'm understanding correctly.

Mika Sinanan: Mika Sinanan. I just want to clarify for Kevin's question, is your decision to pursue this because of the seizures or because of the developmental delay, or is that a more global question? You can't say.

Amy Yuen: It depends on the child.

Mika Sinanan: Okay. So, how severe... so, maybe child... let's take away the seizures. They are severely delayed. They are floppy. They can't, at the age of two, they can't roll over. What is going on here? In that case, we might also think about that, too.

Gregory Brown: Kevin, this is Greg. I guess, the way I view medicine is, patients come in with symptoms. We give them a diagnosis, hopefully, and then we look for treatable causes of that diagnosis, and we look at tests that will give us the most common causes, and then increasingly escalate our testing typically to find other causes. So, there's thresholds of all those level and it depends on the disease. It depends on the long-term morbidity and mortality of that disease. So, it's not simple, and so anyway, that's how I'm viewing this discussion. I don't know if you view that differently. So, I agree with you. I don't think this is being used to make the diagnosis of autism spectrum disorder or developmental delay or intellectual disability. It's once we've made that diagnosis, is there a significant percentage of treatable causes that we think it's worth saying this is a tool that physicians need in their diagnostic kit.

Seth Schwartz: This is Seth. I think that's an important question, though, that's not been answered. So, we're saying that this is not being used to make the diagnosis. So, if that's the case, then we could specify that you can only use this testing in kids in whom the diagnosis has already been established, but I think that the reason that we're talking about this is because there's a significant chance that people are using it to make the diagnosis in kids where they are not as clearcut either, if you have a kid who maybe has a little bit of developmental delay, maybe has some behavioral issues, maybe you're not sure what's going on, are people using this test to sort that out? So, I think that's the area where there's the potential for explosion of this testing. Maybe it's good for that, but I don't think that we saw any evidence it's good for that, but it's a pretty good test. It seems like if you have this, these deletions there is a pretty strong association with these conditions. So, maybe it's good for that. The incidence in the general population is very low. So, it's probably not a good screening test, but I think that's part of what we need to sort out, as a group today is,

where should this test be used, and that's where I think we're struggling with, because it's not clear how it is being used.

Gregory Brown: To me, the answer is, the State came to us with a question. Their recommendation is that it should be considered in patients with developmental delay, intellectual disability, multiple congenital abnormalities, and autism spectrum disorder. So, once a clinician has made those diagnoses, they're asking if that's an appropriate test. Their concern was, is it being ordered on someone that comes in with a one-month delay at 11 months old. So, I guess, we're to respond to their question. Their question is not, should this not be used in anybody. Their question is, is this an appropriate subset of patients to order this testing. Do other committee members see the question differently?

Mika Sinanan: Are you regarding key question number three?

Gregory Brown: No, I'm ask... again, the State picks these topics, and they pick the topic, and they gave us a recommendation. . .

Mika Sinanan: But key question three says, for what conditions should this be done.

Gregory Brown: Well, right, if any, correct. Yeah. Well, so, this [inaudible] efficacy here. Any other additions that we add?

Sheila Rege: Well, in response again, and we've discussed this, where is that, does the scientific evidence confirm the use of technology can effectively replace other technologies, or is this additive. In the agency's recommendation, it was first a genetic test and then this. Our expert says, after this test you rarely need a karyotype again, a genetic test. So, there is some language in there so we don't have a lot of double testing.

Gregory Brown: Correct. And I guess I agree with you. I was thinking of that maybe more under cost outcomes or cost effectiveness. In other words, if it's essentially the same cost, there may be situations where if it's just as cost-effective to order CMA versus karyotyping, then... and again, that could be part of the utilization review that we briefly talked about, but we may make that another condition whereas cost-effective as karyotyping, or something.

Amy Yuen: This is Dr. Yuen again. I have another question. On the insurance reimbursement level, do they have any way to track and say this child already had a chromosome array, and now we're seeing a request for a karyotype, and this is the same child, or would that not be detected at the insurance level? Or, for example, maybe they've already had a

chromosome array, and someone didn't know that, and they're about to order it again.

Gregory Brown: There's your analytics person there.

[Person speaking in background – inaudible]

Amy Yuen: There would be a significant cost savings there, because sometimes we'll see children who have had duplicate testing, because different medical providers didn't know that they'd already had testing. In some cases, the testing had been negative, and in some cases they had a diagnosis, and there was obviously no need to rerun the test.

[Person speaking in background – inaudible]

Gregory Brown: Any thoughts on cost-effectiveness.

Sheila Rege: This is Sheila Rege again. I don't know if this is in our prevue, but once the decision is made, either covering it or not covering it, is there a way to look at utilization and have this come back to the committee, as whether the flood gates opened or we were wrong?

Gregory Brown: Well, our topic this afternoon is a re-review. So, if you looked at this down the road and the State wanted to come back and say we've done this. We've implemented the policy. We still have concerns, or there's this issue, they are free to do that. Am I putting words in your mouth?

Sheila Rege: Thank you.

Dan Lessler: This is Dan Lessler, and Josh, I don't know if you want to comment, as well, but really what drives re-reviews is evidence, new evidence. So, your decision today is in large part a clinical decision in terms of what's appropriate for the use of microarray. Josh, I don't know if you have anything to add to that, but that's sort of the context I would provide.

Josh Morse: I agree, Dr. Lessler. If new evidence emerges that could change, that evidence could be a variety of things. It could be new high-quality scientific research, or it could be published registry data, but new evidence is usually the trigger.

Seth Schwartz: So, this is Seth. I think we're kind of circling around this. I'm not sure that we're kind of going in... we're leaning in a direction, so I just would kind of summarize a little bit and maybe this can help to push us. We're starting to talk about conditions, I think. I think the way I would summarize where

I'm... what I've heard so far is, we have a test that has fairly high diagnostic yield in a population where we already suspect that they have the condition. We have some vague understanding of what that population will look like, and we can define it better. There is evidence that having this testing changes management in some way. For us, who are not experts in this field, I think we can speculate about what that really means, but that's all that we can do, but clearly on tests of people who take care of these children, studies on people who take care of these children, they've shown that these tests in a significant number, 50% of kids, changes what they're going to do in some way. So, I don't think there's anything we're going to talk about that's going to change that basic situation. So, maybe we should think about whether that's compelling enough that we're going to cover this technology, and we need to think about just specifying in a better way who exactly we want to make it available to.

Gregory Brown: Okay. Well, any further discussion before voting. I certainly have no, okay.

Josh Morse: So, you have two voting phases.

Gregory Brown: Yep.

Josh Morse: Okay.

Gregory Brown: So, the first voting phase is looking at safety. So, let me take a stab at the safety issue. So, I think in terms of safety there are certainly not doing the testing and not finding a treatable condition is a safety issue. I think there is the more hard to quantify future life insurance, disability insurance, health insurance risks. So, there is certainly both ways. So, if that's an appropriate way to frame the safety question, we can vote as to whether you think that there is... is there sufficient evidence that the technology is safe for the indications considered.

Mika Sinanan: Mika Sinanan. It depends on the population you look at. If it's a very broad population, the safety might change, because then you're assigning diagnoses to people who don't have necessarily clinical indications in the way that, Seth, you have talked about.

Gregory Brown: Actually, I think...

Mika Sinanan: If we're defining a population, then it's a...

Gregory Brown: ...correct. So I, the... again, I think I didn't clarify. So, if there's any population for which you think there is evidence, then you would vote

based on that evidence. And then, when we get to whether we approve or cover or not, or cover with conditions, then we would discuss those populations, okay?

Mika Sinanan: Okay.

Gregory Brown: So, is there any population or subpopulation in terms of technology. Is this unproven, less, equivalent, more in some, or more in all?

Josh Morse: I see three...

Gregory Brown: Four.

Josh Morse: ...four some. Let me go slow, two unproven, and two equivalent. And Dr. Walsh?

Kevin Walsh: Unproven.

Josh Morse: Three unproven. Okay. And I would, related to these questions, I would just remind you, you do have the key questions before your decision tool, and the scope of the report that you're being asked to weigh in on today is defined in the key questions, as far as the PICO. So, the population in consideration here is defined.

Gregory Brown: Okay. So, and...

Josh Morse: Just before your decision aid, if you want to refer back to the key questions and the scope for consideration.

Gregory Brown: Okay.

Josh Morse: It is the document that...

Gregory Brown: Okay. So, our population under consideration is children and fetuses diagnosed with or suspected of having congenital defects, autism, intellectual disability, or developmental disability. Thank you for helping us clarify. So, that's our population. For efficacy and effectiveness, if I heard from you, Seth, the issue there is that you feel... you felt that there was some change in management based on this testing. You couldn't quantify it, but, yeah.

Seth Schwartz: I think there's two things. I think the first is, does the test, is the test... is the yield of the test good? Does the test show us what it purports to show us, and I think the data for that is pretty strong. Then, the question is, does

it change management, and while it's speculative to the extent that we can understand it from what we have, it seems to change management in a significant number of kids.

Kevin Walsh: I would ask that we also consider, does it change outcome.

Gregory Brown: We don't have any evidence there.

Kevin Walsh: Well, we have evidence that there is no evidence. We have evidence that there is no findings that it improves outcome.

Gregory Brown: Correct. Okay. So, unproven, less, equivalent, more in some, or more in all?

Mika Sinanan: What was that question again, like, four?

Gregory Brown: Is there sufficient evidence that the technology has a meaningful impact on patients and patient care?

Josh Morse: So, there are eight some.

Gregory Brown: Dr. Walsh?

Kevin Walsh: Unproven.

Josh Morse: One unproven.

Gregory Brown: And then, our third question is cost outcomes, cost-effectiveness. Is there sufficient evidence that the technology is cost-effective for the indications considered? Again, five options, unproven, less, equivalent, more in some, more in all.

Josh Morse: So, Dr. Walsh?

Kevin Walsh: Unproven.

Josh Morse: Nine unproven. Thank you.

Gregory Brown: So, let's... can we just take a straw poll, in terms of our coverage. Are people... again, my sense was this maybe with Seth's summary, we're leaning towards coverage with conditions. Is that what most people are considering? Okay. So, I'm seeing most people around the table shaking their heads yes. So, should we go ahead and have that vote then. And then we can come up with our recommendations or?

Seth Schwartz: We can do it either way. Sometimes, we define the conditions first when we have the vote, so we know what we're voting for.

Gregory Brown: Well, I guess, if we can have the... I see what you're saying.

Seth Schwartz: Either way. Typically, what we'll do is, since we're actually voting for cover with conditions, and it's a binding vote, we generally want to know what those conditions are that we're actually voting for.

Gregory Brown: I agree. Thank you for clarifying. So, are you doing the honors? Okay. Just for ease, can we start with the State recommendations? So, cover with conditions, genomic microarray for diagnosing genetic abnormalities in children with any one of the following: Multiple congenital anomalies, global developmental delay or intellectual disability, autism spectrum disorder. From our public comments, I heard concern about multiple. Can we just say congenital abnormalities, so whether it's one, two, or five it's not an issue? Any other?

Kevin Walsh: Well, I think the co-... this is Kevin. I think that the recommendation I'm reading says, in addition to what you just read, Greg, it's when the following are present.

Gregory Brown: Yeah.

Seth Schwartz: This is Seth. I would tend to agree. Just saying congenital anomalies seems pretty vague. I mean, if you have a malformed finger that can be a congenital anomaly. Is that enough that you should do genetic testing? I mean, if you want to specify what type of congenital anomalies maybe, but I don't know that we could get into that. It seems like the definition has been multiple congenital anomalies, and that has a meaning within this community that we should take advantage of.

Gregory Brown: Well, we had at least one person from that community that's working clinically and saying that may... anyway. I don't... Dr. Yuen, you're our expert on that.

Amy Yuen: This is also hard, because it depends on the exact anomaly, and I think it would be impossible to make an exhaustive list of specific anomalies. There are some instances where it's one severe anomaly that you might want to do an array for, but one small minor anomaly isn't going to warrant an array. So, the example, if the baby has a missing finger, this is probably not related to a chromosome disorder. He doesn't need an array, but if the baby has a large cleft palate, he might have a chromosome disorder.

There is a significant enough correlation of different chromosome disorders with a cleft palate. So, you might not necessarily need multiple ones, but there are certain single ones you wouldn't test for.

Gregory Brown: Well, so let's leave the multiple for a second. Let's do the... we'll include the targeted genetic testing, as indicated as negative. The clinical presentation is not specific to a well delineated genetic disorder. The results of testing could impact the clinical management, and I think the key word there is could, not will, and then do we want to add oversight, you know? There's been discussion about having some sort of utilization review, not a referral, but a review. Would that... does that make it feel more appropriate to you, Kevin?

Kevin Walsh: I like Kaiser's restriction. They still to it in a way that doesn't say a person has to see a geneticist, per se, but someone with some additional training. I am fearful of allowing people like me to order this test, because I find that this child has intellectual delay or developmental delay. I don't think it's applicable in that situation. So, I think that we have to filter it down a bit. And the question that we've been batting around is how can that be operationalized. It's a difficult question, I agree.

Gregory Brown: Okay.

Amy Yuen: Dr. Yuen again. I agree with your thoughts about Kaiser's phrasing. They use the word significant, and that could help with sorting out the multiple versus the mild versus the severe. The term significant could be used there.

Seth Schwartz: Can we ask our team whether significant is operationalizable.

Shana Johnson: This is Shana. I think significant would be helpful in giving to the agencies the spirit of the policy. I mean, they'll ultimately define what they consider as significant, but I would anticipate that that is a good way of communicating a cleft palate, even if that's the only thing that's there, that is a significant finding, as opposed to an absent fingernail or something. So, I'd be in favor of that.

Carson Odegard: It's interesting that they say dysmorphic features versus genetic anomalies. I kind of question why they would say that, as opposed to genetic anomalies.

Gregory Brown: Well, it says dysmorphic features or congenital anomalies. So, it's either or. It's not and.

Carson Odegard: Okay.

Gregory Brown: Yeah, the... I guess my question is, this just says for ID, which is intellectual disability. So are we talking about expanding it for the three/four that the State proposed, so not just for intellectual disability?

[Person speaking in background – inaudible]

Gregory Brown: Well, right. So, that's what I'm saying. I think we need... I guess I, personally, would prefer to expand it to the three lines that you have in the State's recommendation, not just ID. So, the other thing that I think is significant is results are expected to affect clinical management. That's a very different level than could affect clinical management, because it's already a later test. So, I mean, how probable does it need to be to say it's likely? I mean, theoretically, that's over 51% if it's expected to affect management, and we don't even have a... we've got an 8% yield on autism spectrum disorder. So, I think... personally, I think that that phrase, expected to effect is too strong. I would prefer results could affect clinical management.

Sheila Rege: Sheila Rege. I'm good with that.

Gregory Brown: Actually... so, Chris, I would take out that first targeted genetic testing, as indicated as negative, because that sounds to me like we're forcing them to do the karyotype testing when it may not be the appropriate? Or how would you interpret that?

Amy Yuen: Or maybe if you used the word 'if' indicated. So, if we see the child, and we see something else specifically that we could test for with another genetic test, we run that first.

Gregory Brown: Okay.

Amy Yuen: But if we look at them and we don't see anything else that's indicate first, the 'if' might help take care of that.

Gregory Brown: And I think that can be part of the kind of utilization review that we have under genetic counseling by a healthcare professional. So, it's not counseling, but utilization review by a healthcare professional with appropriate genetic training and experience has been conducted. Is that accepted?

Sheila Rege: What does that mean? Sheila Rege. What do we mean by that, utilization review, rather than just saying genetic counseling is recommended by a

health professional, or what's the difference? Utilization seems to mean that the agency does.

Dan Lessler: I wouldn't recommend using the term utilization review I a decision.

Gregory Brown: Okay.

Seth Schwartz: It seems like this is the utilization review. In other words, these are the points that you need to meet in a utilization review in order to be eligible for the testing. So, we're specifying what those are.

Gregory Brown: Right. Sure. So...

Sheila Rege: This is Sheila again. I wonder if we could say, if available, genetic counseling by a health professional should be conducted, something about if available, so kind of encouraging it in some way.

Gregory Brown: What I'm trying to incorporate here was the public comments where they didn't feel that the state had the capacity for genetic counseling, but they did have capacity for some sort of review, and if utilization review is an appropriate terminology, I didn't mean to pick that. I don't know the... again. So, it seems to me like there's some sort of oversight by someone trained in genetic testing/counseling, as to is this an appropriate test.

[Person speaking in background – inaudible]

Amy Yuen: We have access that if something is found, genetic counseling is available.

Gregory Brown: Correct.

Amy Yuen: Terming it more like that is better.

Gregory Brown: That's after the fact. I guess, so that doesn't...

Amy Yuen: What that is saying is, if you don't have the... it's more, like, how do I say this? It's more prioritizing that you should be thinking about that, that if your clinic isn't set up to access that and get patients access for that, then you shouldn't be ordering the test. So, it's more of a symbolic recommendation. I just meant to clarify what the state resources are, as far as availability for genetic counseling, that we could... that there is enough providers to provide it if an abnormality is found, but not to send every child who may need the test to it before the test can be performed.

Gregory Brown: Okay.

Dan Lessler: Dan Lessler. I just want to clarify that last comment about a genetic counselor being available to help post-test. We're not saying that that would be a required aspect in order to... as... we're just saying...

Gregory Brown: To me, that's out of scope.

Dan Lessler: ...right.

Gregory Brown: Is that what you're saying?

Dan Lessler: Well, I think the idea is that it would be helpful for people to be considering what are they going to be doing with the test and what kind of expertise is going to be available to help with its interpretation and counseling of the family, but yeah.

Gregory Brown: Well, again, that's after the test has already been ordered and done. So, is that... I mean, we're here to support you. So, again, to me, that's out of the scope of this question, because that's saying once the test has been done, what is the treatment? So, what I was trying to address were the comment by Kevin saying he didn't feel he had the qualifications to order these tests and our public comments saying we don't have capacity for everybody to be seen before the test is ordered, and is there some mechanism by which if the test is ordered, and it's inappropriate, is that... would that occur internally within the State to say this isn't... it doesn't meet these criteria. That's what I'm trying to figure out.

Dan Lessler: It wouldn't be a mandate, but if you find something, I mean, it'd be nice to think about, I'm ordering the test and if I find something that looks... I don't have the expertise to explain what the heck that means, I'm thinking about ... I'm ordering it, and I think I have some expertise available and a genetic counselor, so just... it's just a teaching point, really, for people that are considering ordering the test. It's not a mandate.

Sheila Rege: This is Sheila. And I think Greg is looking for before, and that's why softening it by saying if available, maybe assessment by a healthcare professional with genetic training is encouraged. Is that... or can that just be in the intent. I mean, I just...

Mika Sinanan: Mika Sinanan. I have another way to get potentially at that. If we said, and I think Dr. Johnson, you made the point about why you chose global. Global developmental delay or significant intellectual disability gets around the issue of minor or trivial or very early. So, significant becomes helpful. In the next line, if we were to say clinical diagnosis of autism

spectrum disorder then who has made that clinical diagnosis? Is Kevin going to be making a diagnosis of autism disorder? Somebody would have to say, I have enough comfort and skill and experience and training to make that diagnosis or they refer to a specialist to make that diagnosis. So, by the listing of these and the specification, we drive them to do the right thing rather than say, well you ought to consider genetic testing, 'cuz it'll be very hard to say... to operationalize that I think.

Gregory Brown: Instead of significant, I don't know what that necessarily is. Can we say moderate or severe as opposed to... that doesn't include minor.

Mika Sinanan: I would ask Dr. Yuen about that. What we're trying to do is to avoid the trivial examples that we've heard of somebody who is a month off of the normal curve, as opposed to something that is significant, but obviously, it's a subjective decision.

Gregory Brown: Well, I don't think a month off the curve is any intellectual disability is what we're saying.

Amy Yuen: Normal development.

Gregory Brown: Normal variant of development. So, the significant probably... it's either... if it's going to be diagnosed as intellectual disability, it's already significant. Is that what?

Amy Yuen: I would think, when you get to the point of using that term, it should be significant or you're not going to use that term?

Seth Schwartz: I think similar to what you said about clinical diagnosis of autism, you could also say clinical diagnosis of intellectual disability because significant is relevant in the terms of a parent whose kid is a month delayed who is really concerned, that might be significant. So, who is making the, who is defining significant. So, I think by saying clinical diagnosis or something similar that would get around that problem.

Kevin Walsh: I like Mika's inclusions, because what I'm fearful of is, the way Gary proposed it, there's no gate at the beginning. I can order this test any time I want if a child is one month off the developmental milestones and the parents lean on me hard enough. So, I'm trying to put some wording into this that avoids that situation, and I think that we know that there's not genetic expertise applied in this State to put the gate there. So, I think Mika's wording does create some kind of restriction that is operational.

- Gregory Brown: I guess the other question... I agree with you, and we're all... the question is, we're already in the healthcare system. So, they're not going to... they have a clinical diagnosis. I mean, it is a clinical diagnosis if they're in the healthcare system. Am I misinterpreting?
- Kevin Walsh: Well, no. That's not true. I mean, I do well child checks all day long on normal children.
- Gregory Brown: Right.
- Kevin Walsh: They're in the healthcare system.
- Gregory Brown: Well, right, but I'm saying is if you diagnose them with developmental delay that is a clinical diagnosis, 'cuz you're in the healthcare system. So, I mean, I guess the issue is, if you have a school psychologist that's in the education system and says that they're developmentally delayed, can that trigger this test, or does it need to be a physician that orders the test and therefore, give them a clinical diagnosis? That's a question.
- Mika Sinanan: So, Mika Sinanan. Part of this is social engineering. It's driving people to think about it in a slightly different way. By putting the terminology of clinical diagnosis, it's no longer just, like, if you order any test nowadays, you have to put a clinical diagnosis attached to it for medical necessity, right? So, it would be easy to say, well, okay. Why am I ordering this? Well, developmental delay goes on the problem list, but that's what we're talking about is the patient has an established clinical problem that we're trying to sort out, not just a justification for the test. I think that this helps them see not just the justification but actually a clinical problem that we're trying to solve.
- Gregory Brown: Dr. Johnson has a comment?
- Shana Johnson: Yes. I just wanted to confirm with Dr. Yuen, my understanding is that the term global developmental delay, as understood, means that there are two standard deviations or greater off the normal curve in greater than two areas.
- Amy Yuen: I think of it most [inaudible] we've got multiple areas involved. So, we've got motor delay and speech delay. So, that adds to describing the significance of what's going on with the child.
- Shana Johnson: The two standard deviations, which is encompassed by using that term global developmental delay that kind of makes it so that you're testing the

kids with the moderate to severe phenotypes, not the ones who have normal variation in development.

Amy Yuen: Yes. That would help weed out the ones that were just on the wider end of the normal range.

Shana Johnson: Yes.

Sheila Rege: Sheila Rege, but it's an or there. It's global developmental delay or whatever form of intellectual disability, be it mild, moderate, severe.

Shana Johnson: Intellectual disability's formal definition is, from the DSM-V, is also two standard deviations or, like, an I.Q. of 70 or less, along with inability to function in a couple of different areas. So, it's just the age. Global developmental delay is less than five, and intellectual disability is that same level of impairment greater than five when you're more confident, because they can participate in testing better and all those things.

Amy Yuen: So, it's basically a big kid, little kid designation.

Sheila Rege: So, it is a DSM-V diagnosis, or whatever the DSM is now currently.

Shana Johnson: Yeah. And that's why I specifically used those terms was because they have those well-accepted objective definitions that put the kids into the more moderate to severe phenotype to make it more clear of when the evidence supports this test being medically necessary.

Laurie Mischley: This is Laurie. I'm on board with what we have. I think we're... did we ever clarify multiple congenital anomalies versus a significant single one? Did that...

Gregory Brown: Well, we had talked about using the Kaiser term significant dysmorphic features or congenital anomalies, and do we want to do that instead? Everybody agree with that? I'm seeing shaking heads. Yep. Okay. So, significant dysmorphic features or and then just, yeah, congenital anomalies. Okay. So, targeted genetic testing if indicated, is negative. So, that doesn't force us to do karyotyping. Clinical presentation is not specific to a well-delineated genetic syndrome. Results of testing could impact the clinical management, and then, I'm hearing we're not going to specify any sort of review or... and the counseling. Do we want to comment on that or leave... I mean, that's... it doesn't affect the testing. Okay. So, are we ready to vote? Okay. Kevin, can you see the screen, or do you...

Josh Morse: He is not seeing the screen.

Gregory Brown: Okay. So, I just read it, Kevin. Does that, do you have any questions or?

Kevin Walsh: No. Thank you, Greg. I'm good.

Gregory Brown: Okay. Then, cover, not cover, cover with conditions.

Josh Morse: So, I see eight cover with conditions here, and Kevin? Dr. Walsh?

Kevin Walsh: Cover with conditions.

Josh Morse: Nine cover with conditions.

Gregory Brown: Okay. We're unanimous. Time for lunch everybody. Thank you. So, we should reconvene at we've got 12:30. How about we take 12:35, give us 25 minutes? Okay. Thanks everybody.

Josh Morse: I'm sorry. We failed to ask the two questions related to national coverage determination and...

Gregory Brown: Well, Medicare has no coverage decision, because it's pediatrics.

Josh Morse: Thank you.

Gregory Brown: And so the second coverage decision was?

Josh Morse: The other question relates to existing professional guidelines, and does your decision differ from expert guidelines? If not, what evidence did you rely upon to deviate from those?

Gregory Brown: So, I think there are...

Josh Morse: I have the expert guidelines in your decision tool.

Gregory Brown: Yes. There are several different guidelines, and they are not unanimous. So, I think we are consistent with some of them would be the best way to say.

Josh Morse: I believe you're consistent. Agreed. Thank you, very much. I apologize.

Gregory Brown: Nope. Thank you.

It is time to resume this afternoon. Welcome everybody back. This afternoon, we are going to be looking at the continuous glucose monitoring and update. So, we can start with the State's presentation.

Dan Lessler:

Alright. Well, I'm Dan Lessler. I'm the chief medical officer at the Health Care Authority, and I wanted to give the agency medical director's perspective on continuous glucose monitoring. So, to just begin in terms of the nature of the technology, continuous glucose monitoring provides real time information about glucose levels that, when correlated with diet and physical activity and such, can enable better glucose control in patients with diabetes. The technology, and I think when we hear the in-depth presentation from the vender, I actually have some pictures and so forth, but essentially, the way this works is that there are measurements that are taken from interstitial fluid and ultimately transmitted to a receiver, which provides the glucose level and the technology allows, well, actually now there are different types, but the technology allows for measurement on a frequent basis of glucose in the interstitial fluid. There is a slight lag between the level and glucose and in plasma. Then, distinct from the continuous monitoring that has alerts and so forth and actual real-time display, there also is what is called flash continuous glucose monitoring where there are no passive alerts, and basically the data is available when a sensor is scanned. That's how the results of the glucose is received.

Today's report, actually, is an update on a report from 2011. That 2011 report focused on self-monitoring of blood glucose, which included continuous glucose monitoring in people 18 years of age and younger who required insulin. Today's update includes that population, but other populations, as well. So, it's quite a bit more extensive in terms of what's being included. So, we're looking at real time continuous glucose monitoring in people of any age with either type 1 or type 2 diabetes and in women with diabetes during pregnancy.

From the agency medical directors' standpoint, as we were thinking about this and just categorizing these different aspects of the technology, we categorized concerns about safety as being medium and efficacy and cost being of high concern.

This is just a list of the key questions that were considered as part of this technology review. What is the evidence of efficacy and effectiveness of continuous glucose monitoring? What is the evidence of the safety of continuous glucose monitoring? What is the evidence that glucose monitoring has differential efficacy or safety issues in subpopulations? What is the evidence of cost-effectiveness of glucose monitoring? The

PICO or population intervention comparison inclusion criteria are people with diabetes type 1 or type 2 and pregnant women with preexisting diabetes or gestational diabetes was the population. The intervention that's being considered is FDA approved continuous glucose monitoring. The device is an FDA approved combination devices integrating real time continuous glucose monitoring with an insulin pump. Then, the comparator is self-monitoring of blood glucose, attention control, blinded, or sham and usual care. Those were all possible for comparators.

This is, I know, just a rough number for continuous glucose monitoring costs. I know these are actually changing, probably even as I speak, but on the order of \$1000 give or take, and then there's costs of ongoing supplies that are several hundred dollars a month.

The next couple of slides just show the costs to the agencies with respect to continuous glucose monitoring. First, here, you see a cost for the Uniform Medical Plan, and you can see over the last four years, costs have continued to grow year over in really all the different categories, such that over that four-year period of time, spend is about 2.5 million dollars, but a little over a million dollars in the last year. Considerably higher in Medicaid. We actually have three years of data. There's some problems with the 2013 data. So, we can't give you the full four years that we provided with Uniform Medical Plan, but you can see the costs are a much larger population and the costs are considerable over the last three years, over 7.5 million dollars.

So, what I'd like to do is really in light of the fact that we're going to have the vender speaking to the detail of the evidence in a deeper dive, really just step back for a moment and sort of from our perspective try and summarize sort of a take home, as we look at the materials that have been provided by the vender. Then, talk about the coverage criteria of national bodies and of other payers. Then, close with the recommendation of the agency medical directors.

So, here I'm beginning just with overall summary of continuous glucose monitoring in people with type 1 diabetes. First, children and adolescents 18 and younger that should say. Again, the gestalt for us is that continuous glucose monitoring improves A1c control in the short-term, but that the evidence for longer term, and even then, talking relatively short-term, out to six months or a year is less strong. In adults, continuous glucose monitoring improves blood sugar control up to a year without worsening hypoglycemia. In adults, it appears to reduce the time spent in biochemical hypoglycemia at three and six months, although there is really no good data on more severe hypoglycemia, likely because it's a relatively

rare event in terms of what you're going to catch around the context of the clinical trials that have been done.

In adults with type 2 diabetes, there is evidence for improvement at three and six months, but really not good evidence in terms of impact on hypoglycemia. With respect to continuous glucose monitoring in women who are pregnant, first those with type 1 diabetes, this is probably where the best evidence is, and there is evidence that it decreases C-section rates, decreases admissions to a neonatal ICU, although it does not appear to have an impact on time spent in hypoglycemia for women with... well, actually it's for both women with preexisting type 2 diabetes or gestational diabetes. The evidence is really insufficient to conclude one way or another around its impact on clinical outcomes.

Finally, with respect to the Flash devices, these are the ones that you put the sensor over to actually read on an ad hoc basis. There's just very limited data with respect to those, which is summarized here, both in terms of the impact on blood sugar control and on hypoglycemia.

With respect to safety, you know, overall I think the... just the high level summary here is the devices appear to be relatively safe. The common adverse effects tend to be minor and skin related. I do think it was interesting that at this point in terms of actually being able to get a good handle on the impact of device malfunction and so forth, relative to safety, that there really isn't great data on that for various reasons, not the least of which is, it's not being really collected on a standardized kind of a way where you can get good denominator information on how many people are using these and then relate that to the number of adverse incidents that occur because of malfunction, but overall appears to be relatively safe as a technology.

Then, just by way of context, the trials that were reviewed for the most part are conducted in an efficacy context and not really in a real outcome or pragmatic trial kind of approach, although there was one recent trial that was a bit more pragmatically oriented, I'd say. So, this is just a question of whatever you're seeing in these trials in terms of efficacy, you know, to what extent does it translate into the real world. There are questions around which patients may benefit most from continuous glucose monitoring. Certainly, the available data, I'd say, just again the gestalt from the report would seem to suggest that people who use it regularly, more than half the days of the week or more, appear to be the ones that benefit, but then, also the questions of patient motivation, education, self-management, and relationship of those aspects to clinical outcomes. There really are no longer term clinical studies that are in an

RCT context. There is observational data. So, the longer term outcomes really are not well defined at this point. Then, there is no long term data on disease outcomes, although I would add that those would be very hard to obtain, because they would require a very large trial and a long period of time and I think, generally, A1c control is now a very well accepted surrogate endpoint for diabetes in terms of clinical outcome.

Then finally, this is, as we've seen just in the last few months, a rapidly changing area in terms of technology with new technology sort of continually coming out and the available of that technology often outpaces the available data to understand the impact on the outcome.

With respect to cost-effectiveness, there is some data, but as was noted in report, really, I would note two things. Most of this data comes from studies that are funded by industry, and there are a number of assumptions that are made, such as that the benefit of monitoring on glucose control accrues over many, many years. Really, the data we have is much shorter term than that. Having said that, with favorable assumptions, the continuous glucose monitoring appears to be cost-effective, assuming cost-effectiveness ratio or a willingness to pay of \$100,000 per quality adjusted life year.

What I want to do now is just touch upon some national guidelines and recommendations and then look at some of the recommendations for parameters used by various payers. This is beginning with the Endocrine Society in Children, and here the recommendation is that real time continuous glucose monitoring be used by children and adolescents with type 1 diabetes who have achieved glucose control or an A1c of 7%, because it will assist in maintaining target A1c levels. Then, likewise, it is recommended in the same population for people who are not in as good control. There is no recommendation for children less than eight years of age.

The Endocrine Society for Adults, you can see here that their recommendations, again, recommended for adult patients with type 1 diabetes who have A1c levels that are above target and who are willing and able to use the device on a near daily basis and likewise in people with well-controlled type 1 diabetes who are willing, again, to use it on a daily basis. Then, there's a recommendation for short-term intermittent continuous glucose monitoring in patients with type 2 diabetes who are not on prandial insulin who have A1c greater than 7.

This is the recommendation from the American Association of Clinical Endocrinologists and the American College of Endocrinology. Continuous

glucose monitoring should be considered for patients with type 1 diabetes and type 2 diabetes on intensive insulin therapy to improve A1c levels and reduce hypoglycemia and continuous glucose monitoring may benefit patients who are not taking insulin.

Finally, just one recommendation, again from the Endocrine Society, and this is from 2013, in terms of diabetes and pregnancy. It is suggested for use during pregnancy in women with overt or gestational diabetes when self-monitored glucose levels or A1c values in women with overt diabetes are not sufficient to assess glycemic control.

The Medicare national coverage decision on continuous glucose monitoring is a little bit complex I would say. So called nontherapeutic continuous glucose monitors that are used as an adjunct to self-monitoring are not covered, and that would be monitors where the blood sugar that is indicated cannot be used for making dosing adjustments of insulin. On the other hand, now, there are so called therapeutic continuous glucose monitors that are available where the FDA has certified them such that they can be used for making therapeutic decisions. There are two such devices that are available, and those are covered by Medicare, presumably because they replace the cost of standard blood glucose measurement and the multiple sticks that would need to occur, since they can be used to adjust dosing the insulin. What I want to do now is just take a look at some of the current coverage parameters of health plans and first, I was going to begin here with Kaiser Washington, formerly Group Health Cooperative. So, Kaiser covers continuous glucose monitoring for people with type 1 and type 2 diabetes who, despite adherence to appropriate glycemic management and appropriate glycemic management plan, which includes customized basal bolus insurance regimen, testing of blood sugar four or more times a day, competent problem solving skills, carbohydrate counting, and appropriate meal management. So, in those. . . that group who have a history of hypoglycemic awareness within the past three years resulting in frequent and severe hypoglycemia, or a history within the past three years of frequent and severe hypoglycemia, and the request in this case must be made by an endocrinologist.

This is Blue Cross/Blue Shield, continuous glucose monitoring may be considered medically necessary for patients with type 1 diabetes who have demonstrated an understanding of the technology, are motivated to use this advice, are expected to adhere to a comprehensive diabetes treatment plan supervised by a qualified provider and are capable of using the device to recognize alerts and alarms, or patients with type 1 diabetes who have recurrent, unexplained hypoglycemia or impaired hypoglycemic

awareness, and in patients who have poorly controlled type 1 diabetes who are pregnant.

This is the decision that the Health Technology Clinical Committee rendered this committee back in 2011 for people under the age of 19 with respect to continuous glucose monitoring. That coverage decision reads accordingly: Continuous glucose monitoring is a covered benefit for diabetes patients under 19 using insulin when the following conditions are met, suffering from one or more severe episodes of hypoglycemia or enrolled in an IRB approved trial.

So, with that as background and acknowledging that this is a rapidly developing area, both in terms of the technology, as well as evaluative science, this is where we have landed in terms of a recommendation to the committee. Continuous glucose monitoring is a covered benefit for children and adolescents under 19 with type 1 diabetes when the following conditions are met: Unable to achieve target A1c despite adherence to an appropriate glycemic management plan, as defined, or suffering from one or more severe episodes of hypoglycemia despite adherence to an appropriate glycemic management plan, or inability to recognize or communicate about symptoms of hypoglycemia. So, that's in the younger population. In adults with type 1 diabetes, continuous glucose monitoring, the recommendation is that continuous glucose monitoring be a covered benefit for adults with type 1 diabetes when the following conditions are met and again, quite similar to those previous; unable to achieve target A1c despite adherence to an appropriate glycemic management plan that involves intensive testing such, suffering from one or more severe episodes of hypoglycemia despite adherence to an appropriate glycemic management plan, or inability to recognize or communicate about symptoms of hypoglycemia.

Then, finally, likewise in people with type 2 diabetes. So, really the same as the previous recommendations. In pregnant women with diabetes, we would recommend covered for pregnant women with type 1, covered for pregnant women with type 2 diabetes on insulin prior to pregnancy, cover for pregnant women with type 2 diabetes whose blood glucose does not remain well controlled, defined as A1c above target or experiencing episodes of hyperglycemia or hypoglycemia on diet and/or oral medications during pregnancy and requiring insurance. Then, covered for pregnant women with gestational diabetes whose blood sugar is not well controlled and with the similar as above for women with the type 2 diabetes.

At this point, from what we've seen just in terms of flash devices, we would recommend that they are not covered, since there isn't the evidence base yet that there is around the other type of [inaudible]. So, with that, I'll give it back to Dr. Brown.

Gregory Brown: Thank you, Dr. Lessler. Can I ask a question? So, the flash doesn't have continuous readout. Is it implanted so that you don't have a...

Daniel Lessler: Yeah. It's sort of similar to the other one, it's just that it doesn't have the continuous readout, and you have...

Gregory Brown: Okay.

Daniel Lessler: ...but it's something [crosstalk].

Gregory Brown: But it, I mean, it's not implanted. So, you still have the issue of the skin interface and...

Daniel Lessler: Yeah.

Gregory Brown: ...cellulite? Okay. Thank you. Any other questions for Dr. Lessler?

Carson Odegard: Yes. This is Carson. On your utilization data through 2016, apparently there is a lot of growth almost exponentially. Do you have any idea what the train looks like in 2017?

Daniel Lessler: I don't think we do yet for 2017. It takes about three months of lag to get the claims in.

Carson Odegard: Okay. So, not seeing anything on the.

Daniel Lessler: Well, I can't tell you about 2017 yet.

Carson Odegard: Yeah.

Daniel Lessler: Good question.

Gregory Brown: So, once it's covered or a patient says... you determine they're appropriate for this, how does that work? So, I'm... my mother is type 1... was a diabetes, had an insulin pump, was under Medicare, and once she had that pump, every month she got her supplies. She got a new pump on scheduled whether she needed one or not. And the system just, quite honestly, the manufacturer seemed to drive that, because they were... well, she's eligible for these supplies. She is eligible for a new pump, we're

going to send it to her whether she needs it or not. Then, they presumably bill Medicare, because she's already been accepted for this program. How does the State do that? I mean, once they're on it then are they contracted with the manufacturer who sends them supplies every month? Is that ever reviewed? How does that?

Daniel Lessler: Right. Well, I mean, right now, actually we would be on the Uniform Medical side we'd be following the Blue Cross/Blue Regence policy that I showed. I'm not sure if they, on an annual basis or so forth, require updating. I know that, for example, that Kaiser does require some sort of updating, I believe, at six months or a year. And I actually couldn't, I couldn't tell you whether it's required for the individual Medicaid plans at this point. I think that's something that the committee could certainly consider.

Kevin Walsh: Dan, this Kevin Walsh in Ellensburg. I'm looking at the last recommendation, the last condition rather, inability to recognize or communicate about symptoms of hypoglycemia.

Daniel Lessler: Right.

Kevin Walsh: What's the basis for that recommendation?

Daniel Lessler: So, that, for example, hypoglycemic unawareness.

Kevin Walsh: Well, the wording you have is inability to recognize or communicate symptoms of hypoglycemia. And I am wondering what's the evidence for that particular condition being included?

Daniel Lessler: Well, so that's a good question, Kevin. I mean, what I would say is that there's an assumption that in somebody who doesn't recognize, you know, is unable to recognize hypoglycemia, that the technology, which has a monitor, which has an alarm, can help... would be very helpful under those circumstances. I would acknowledge that no such study, at least none was presented, that specifically amongst people with hypoglycemic unawareness, but that is the assumption and the reason for the recommendation.

Kevin Walsh: Thank you.

Gregory Brown: Any other questions?

Female: I just wanted to call out, Dr. [inaudible] your question had been about a pump, a monitor, and I think the same question applies to both but just

wanted to make sure that nobody else got confused about which one we're talking about.

Gregory Brown: Correct. It was about an insulin pump, not a monitor. Okay. Thank you, Dr. Lessler. We will then move to our open public comment period. Do we have... we have a number of people who have signed up.

Josh Morse: Yes. We have 15 individuals currently signed up. We have about 40 minutes allotted for this.

Gregory Brown: Okay.

Josh Morse: It's a little bit more than... it's a little less than three minutes a piece, but I think if we, at your discretion...

Gregory Brown: Okay.

Josh Morse: ...allow three minutes a piece, we'll be at 45 minutes.

Gregory Brown: Okay. Sure. I think that's appropriate.

Josh Morse: Okay.

Gregory Brown: So, do we want to read the list here.

Josh Morse: We'll start with Thomas Walker, Dexcom.

Gregory Brown: There, please.

Josh Morse: And do you have a presentation?

Tomas Walker: I did, but I'm not going to speak to them, in the interest of time, so. So, good afternoon. I'm Tomas Walker. I'm the senior U.S. medical director with Dexcom. I am an employee of Dexcom, as a disclaimer. I'd like to thank the Washington State Healthcare Committee for actually taking the time to review this technology again. Continuous glucose monitoring is really changing the lives of people with diabetes. I heard a comment that there wasn't a lot of information on using this technology in people with significant hypoglycemic unawareness. That actually will be addressed in February at the Diabetes and Technology Conference in Vienna when a study conducted in Germany on 160 people living with significant hypoglycemic unawareness will be presented. So, my comments today, I'd like to focus primarily on the challenges of a metaanalysis. When you're looking at a technology that's evolving as rapidly as continuous glucose

monitoring. So, a good comparison would actually be cell phone technology. So, if you look at a continuous glucose monitor from the metaanalysis in 2006, those devices are not even on the market anymore. This was my cell phone in 2007. It was an analog system with no data capability. This is my cell phone today, and calling it a cell phone today is really doing it injustice. This is essentially a pocket supercomputer with continuous connectivity offering you a touchscreen, a full HTML web browser. If you were to conduct a metaanalysis combining 2007 cell phones and 2017 cell phones, you would have a very different impression on the usability of the technology today. So, technology assessment on continuous glucose monitoring really should focus on current clinical trials using currently available technologies. This would include the Diamond studies, which looked at people with type 1 and type 2 diabetes. The Gold study, which was conducted in Sweden, looking at people with type 1 diabetes on multiple daily injections, and the In Control study, and the recently published Replace BG trial. Current rulings by the FDA and the Center for Medicare Services have now recognized that continuous glucose monitoring is safe for routine decision making for most patients. They've also recognized that people with type 1 and type 2 diabetes on intensive insulin therapy can benefit from this. Current continuous glucose monitoring technology is not 2007 technology, and today's continuous glucose monitoring systems are demonstrating excellent adherence and patients are truly benefiting from them with reduced time spent hypoglycemic. Additionally, patients have the ability, using their cell phone, to share and follow the technology, the continuous glucose monitoring tracing, so you can be aware of what your loved one's glucose is and receive alerts and alarms. In short, continuous glucose monitoring today is improving the life and the quality of care for people living with diabetes. Thank you.

Josh Morse: The next commenter, Catherine Pihoker.

Catherine Pihoker: I, too, thank you for the opportunity here. So, I am a pediatric endocrinologist, and my comments will be focused on the pediatric population. I've been working with children and their families with diabetes for over 30 years. So, I'm going to show some slides from the type 1 diabetes exchange, which is an observational study of over 50,000 people in the United States. This is just... this first slide is showing how continuous glucose monitoring use is increasing. The red bars are from 2010 to 2012, and the blue bars are in 2017, and you can see far more people of all ages are using continuous glucose monitoring and just related to the comment about inability to communicate hypoglycemia, so kids under the age of 6 are clearly not able to communicate that well, and that's why uptake is so high in that patient population, being that much safer.

So, continuous glucose monitoring use is higher in kids who are on pumps. So, that's the red bar versus multiple daily injections, but you can see still 27% of say the youngest population is using continuous glucose monitoring. I should have mentioned, these data were presented just this past fall at an international pediatric diabetes meeting and showed that in all of the age groups by really focusing on the younger people that the A1c was lower in people who are on continuous glucose monitoring. The red bars are non-continuous glucose monitoring users, and the blue bars are people who are on continuous glucose monitoring. This is true for all racial ethnic groups, and the reason I point that out is there are many reports, unfortunately, of poor outcomes in people who are not white, and you can see that technology works, no matter what racial ethnic group you are. I just wanted to quickly show some data from our patient population. So, we, too, so the scale is a bit different, but continuous glucose monitoring use is associated with better A1c. So, the green bars are the A1c of people on continuous glucose monitoring, and the blue bar is non-continuous glucose monitoring, and you can see in each age group, the A1c is significantly lower in kids using continuous glucose monitoring. Then, this last bar is just speaking to, if you don't use it, it doesn't help. So, the yellow bars are showing people who have continuous glucose monitoring but aren't using it, and their A1c's are not significantly better. You can see in the adolescents, it's actually higher, but I would venture to say that they probably started higher, as well. It's just not effected. So, in summary, I think that continuous glucose monitoring not only improves A1c, but it really changes behaviors, and that's what drives the change in A1c. So, when these kids can see what's happening with their glucose, they are more likely to act on it or anticipate and have better control of their diabetes. Thanks for the opportunity to speak.

Josh Morse: Next is Amy Bronstone. Would you please state your... if you have any conflicts and if anybody funded your travel for you to be here today. Thank you.

Amy Bronstone: Hi. Good afternoon. I am Amy Bronstone, and I am a health services researcher and here on behalf of Dexcom, who I consult with. That's the only conflict I need to disclose. I want to thank you for the opportunity to speak to you today. My presentation is going to focus on the potential economic implications of providing continuous glucose monitoring to patients with impaired awareness of hypoglycemia. We've heard that term mentioned a few times now already. This is a physiological condition in which patients have the diminished ability to detect early warning signs of hypoglycemia, and because of this condition, they're at greatly increased risk for developing severe hypoglycemia. I just want to give you a sense of what this looks like in this population in the State of Washington

where you have about 107,000 people who are diagnosed diabetes among whom just under 35,000 are using insulin, and then this group with IAH, which is about somewhere between 20 to 30% of the population, on insulin, is the group that we're focusing on today. Okay. So, as I noted earlier, if you can see on the left, patients with IAH have a much higher risk of severe hypoglycemia, about a 5 to 6 per fold greater risk of these events. In the center here, I want to acknowledge that most severe hypoglycemia... most hypoglycemic events don't require medical care, but there are a substantial proportion that do. So, you can see in type 1, in type 2, the percent of these events that require hospital, ER visits, ambulance care. On the right, we have the average cost for these events. Key assumption that I'm going to be making here is, and all models make assumptions, but is that continuous glucose monitoring reduces the incidents of severe hypoglycemia by about 60%, and this is based on a small double blind randomized study conducted in just this population, insulin treated patients with IAH, and I'm going to call your attention to the 39 million dollars and expenses for emergency care due to hypoglycemia in people without continuous glucose monitoring versus the 16 million who have the technology. When we add the cost of providing continuous glucose monitoring, which is about 12.5 million for those patients, the net savings is 10.5 million. So, even when we include the costs of the technology, there really is a solid economic argument for providing continuous glucose monitoring to this high risk population. Thank you.

- Gregory Brown: I guess, sorry for the confusion. I think the intent of the public comments are from the public. Having two different people from the same company stand up and speak is not to the point, I guess, from my perspective. I don't know what the rest of the committee thinks, but I think there is also more than one speaker from other companies. So, if there's any company represent-, people from companies here whether you work for the company or consultant, I think you can have one person speak for your three minutes, but not multiple people from the same organization, please.
- Josh Morse: Next up is Molly Carlson. Not here? Okay. Thank you. Dr. Hegazi? He's not present either? Okay. Thank you. Zoe Alfaro?
- Zoe Alfaro: Hi. My name is Zoe Alfaro. I'm sponsored by Dexcom. I was diagnosed...
- Gregory Brown: I, I'm sorry. So, if you're being sponsored by Dexcom, they've already had two speakers. So, well I understand, I mean, what does the rest of the committee think? I mean, this isn't my decision. Okay. Go ahead.

Zoe Alfaro: Okay. Hi. My name is Zoe Alfaro. I was diagnosed later in my life, at age of 18 years old. I just started college away from my friends and family. Student life is already busy enough without type 1 diabetes, but having it, it can easily to a big disaster than can happen when you least expect it, and with my daily life, as a college student, my blood sugars can be all over the board. My parents letting me go several states away from home, can be very scary, but with the continuous glucose monitoring I can see it on my personal phone and share it with loved one. With the Dexcom technology, the data can be shared with five people. It will automatically test your blood sugars. It gives my parents a piece of mind that they can monitor my blood sugars while miles away, but when I was on shots, I had more high to lows, but the really scary thing was, I did not have the technology to help me catch them before it was too dangerous. I was getting up at 2:00 a.m. every morning and waking my roommate up just to make sure that I'm not low or too high. After getting the Dexcom, I feel safer, and I have more freedom, because I do not have to test every moment when I'm feeling off. Now, I can sleep longer, because there are alarms that will wake me up if something goes wrong. Now, three years later, when I don't want to wear the Dexcom for a day or even an hour, for any reason, I keep wondering what my numbers are. I feel like I have less control over them. One moment when my continuous glucose monitoring saved my life was two summers ago when I had a great opportunity to work in Nebraska many states away from home. This job was a very active job, and one night I was asleep, and my continuous glucose monitoring was going off, but luckily my parents were sharing my numbers, and I was at 80, then I went to an urgent low, which is below 55. Luckily, the people helped me wake up and grab a quick snack so I could be standing here today. If I did not have it, I would not be here. One thing about type 1 diabetes is, that others do not understand, is I did not do anything wrong. It's just how my body was acting. Without my continuous glucose monitoring, I do not feel like I can have a normal life, as a college student and a young adult. Thank you for your time.

Josh Morse: Richard Hellmund.

Richard Hellmund: Hello. I'm Richard Hellmund. I'm an employee of Abbott Diabetes Care, based in Oakland, California. I really only have one thing to say, which actually was on one of the slides already, just to say that the Freestyle Libre continuous glucose monitoring system from the beginning of this year, is being reimbursed by CMS through Medicare. So, that was already there. The other thing I just wanted to clarify was that while Freestyle Libre, I think the statement was it doesn't have a continuous readout. And when patient use is they [inaudible] or their cell phone. They do get a continuous record going backwards of their historic up to eight hours, but it's sort of

passive. So, they, you know, they choose to scan. So, I just wanted to make sure that was clear, because sometimes there's some confusion about the differences between the technologies. That was it. Thank you, very much.

Josh Morse: Irl Hirsch.

Irl Hirsch: Thank you for the opportunity to speak. I am not a consultant to Dexcom. Much of my research are many of the trials you've heard. JDRF holds a charitable trust, ADA, NIH, we are currently doing an artificial pancreas trial with Medtronic, just to make sure.

Clarification on hemoglobin A1c, this was a study we were part of back in 2008. We published this putting continuous glucose monitoring on over 500 people. You can see for each hemoglobin A1c level there is an average A1c based on continuous glucose monitoring. The problem is, there is a huge variation for every level of A1c. So, somebody could have an A1c of 7 and average glucose of 180 and someone else could have an A1c of 9 and an average glucose of 175. The point is, there's a huge range of where these A1c levels are. So, when you're dealing with a person, and you're trying to get an A1c target, you may really miss the boat, unless you have the continuous glucose monitoring. So, historically, A1c has been our treatment target, and really, for the past 35 years. Is that appropriate, and is it safe. Well, I think it really depends, but we're learning about the limitations of A1c. Just to point out, hypoglycemia is not a trivial issue. Mortality, no matter study we look at, between 5 and 10% of patients with type 1 diabetes, actually this is how they die. Now, these are data from the T1D exchange. You heard a little bit from Cate about this. The point is, no matter what age the individual, the longer the duration of diabetes, the greater the risk of severe hypoglycemia, which in this study we did as defined as a seizure or a coma. Seizure or a coma. So, if you've had your diabetes over 40 years, the risk of seizure or coma without continuous glucose monitoring is about 20% per year, and those are the white bars there. Ladies and gentleman, this morning, I received a note that Chief Justice Sonia Sotomayor had an episode of severe hypoglycemia. She has had type 1 diabetes, since she was a child, and I know she wasn't a continuous glucose monitoring a couple of years ago, and my guess is, she wasn't this morning. So, given the limitations of A1c and the dangers of hypoglycemia in both type 1 and type 2 patients, wouldn't it make more sense to treat the glucose instead of the A1c. This is the big issue we are having now at the UW, trying to get people to treat the blood sugar. You saw this slide before from Cate looking at how continuous glucose monitoring has increased over the last few years, but I want to point out that right now, as of this month in the University of Washington Diabetes

Care Center, we now have about 60% of our patients using continuous glucose monitoring, because of the flash glucose monitoring, and I also want to point out that these data, with the 24% of the over 65-year-old age group, that did not include the Medicare patients. So, that number is much higher now. You saw these data. This is based on over 16,000 patients with lower A1c. Now, this is not a randomized trial, but I picked... the day I put this slide together, I saw 14 patients this day, 10 with type 1, 7 of the 10 were on continuous glucose monitoring; 1 of the 3 type 2s were on continuous glucose monitoring. I need to stop, and I just want to show you, this is what we see. This is the kind of data that we see and how we can help our patients. Last slide, treat the glucose. We do that with continuous glucose monitoring, not the A1c. For every complex problem, there is an answer that is clear, simple, and wrong, and diabetes, especially type 1, is complex. Not having access to continuous glucose monitoring right now is wrong. Thank you.

Gregory Brown: So, those are the people that have signed up ahead of time?

Josh Morse: Correct.

Gregory Brown: Okay. And now, we have additional people.

Josh Morse: We have day of signups now.

Gregory Brown: Okay. Next.

Josh Morse: Curt Budall? Not speaking? Thank you. Edward Lacava?

Edward Latarn: Good afternoon, panel. Nice to meet you. I am Edward Lacava. I am past chief of medicine for Evergreen Health and chief of endocrinology for the last 20-some odd years, speaking that to my success recently. My goal is to really talk about the real world experience. We'll see data, too, Dr. Hirsch and others who have done an eloquent job. Basically, when you think about by the year 2050, 21 to 33% of the United States population will live with diabetes. The impact of this disease is growing. It's significant, well over 29 million have it today. What we've done in our real world experience, which has grown tremendously, is we've seen basically all aspects of adult care, type 1 with pumps, without pumps, pregnancy, elite athletes, which is an interest of mine, world travelers, and, of course, inpatient and was brought up earlier the issue of what happens immediately post-discharge, the tremendous vortex of decrease in insulin requirements and the significant risk of hypoglycemia, as some of you on the panel are well aware. We spoke to the Diamond study, which was briefly alluded to by the industry experts, which was extraordinary. I think

the things that I want to share with you, in the practice of medicine, I have, in my panel, well over probably 15,000 patients living with diabetes that I've cared for. It has made a significant difference in the morbidity/mortality of this disease. We are, as you are, very concerned, ultimately, about the experience of safety, effectiveness, and certainly value, and we measure that very carefully in our context of situations that we see. We have seen reductions of risk, especially in our high risk patient group that we see on a daily basis. We've seen population benefit specifically in my group of women living with diabetes and pregnancy, who are at high risk individuals who, as Irl mentioned, had lived with this for many, many years. And also, my elite athlete population. It has allowed them to completely change the context of their lives. In the one minute remaining, I must say that the quality of life that hasn't really been addressed, because it's hard to, and because of the rapid evolution of this science, I will tell you, patient after patient who has experienced the benefits of continuous glucose monitoring have reflected to me, it's made a real difference in their lives. So, in summary, this is an issue that helps focus in on prevention, the duration severity and frequency of hypoglycemia, and certainly improves the quality of life, and I suspect over time, we are going to see a dramatic improvement to microvascular complications. Thank you for your time. I think I'm listed twice, so I will seed that time to one of the other people if they need it.

Josh Morse: Thank you. Jennifer Cruz. Can you tell us who you're representing?

Jennifer Cruz: I'm just a patient.

Josh Morse: Gotcha. Thank you.

Jennifer Cruz: Hi. My name is Jen Cruz. I live in Redmond, Washington, and I am a clinical social worker. I have had type 1 diabetes for 17.5 years now. Over the almost two decades of type 1, there are three dates that stand out to me. The first was July 25th, 2000. This is when I was diagnosed with diabetes. It was just handed to me. I didn't deserve it. I didn't cause it, but I took the diagnosis and went running, making the most of it. The next date was November 21st, 2013. This is when I received my first Dexcom continuous glucose monitoring. I went from seeing snapshots of my blood sugar every few hours via fingersticks to seeing a movie of what was happening with my sensor glucose from minute to minute. This gave me a sense of confidence I never had before in the previous 13 years. I felt willing to try new things, because I knew I could see my glucose values and take action, as appropriate. The best thing was, the Dexcom would alarm me when I was going high or low. Having low blood sugar during the day is extremely annoying and an inconvenience, but having low blood sugar in the middle

of the night is terrifying, especially when you live alone. If my blood sugar started to drop, the Dexcom would alert me so I could get some juice. When you're awoken from a deep sleep, you are already groggy enough, but when you also have low blood sugar, it's a really disorienting experience. I know the Dexcom has saved my life several times, and it's much cheaper than a visit to the hospital. The third and final date that stands out to me, so far, is August 31st, 2015. This is the day that I started using the Medtronic Guardian Sensor 3 with the 670G hybrid close-looped pump. This insulin pump takes the data from the center, and it automatically adjusts the background insulin that's delivered to me. I was in college when I was diagnosed with type 1. So, I was pretty much on my own. My parents didn't have to know how to help or take care of me. It was a very lonely experience. Now that I have the Guardian Sensor 3 and the 670G, it's, like, someone finally has my back. Someone, or something, is watching out for me and actually helping me. My cognitive burden has greatly been reduced, and my quality of life has improved tremendously. I have had this awesome sense of freedom. I've worked while having type 1. Speaking of nighttime, when I go to bed now, I don't even think about what will happen in the middle of the night. I don't worry about whether or not I will wake up in the morning. I have had five to six lows at night within the last 874 days of wearing this pump compared to five to six night time lows a week before a sensor and pump. I know the sensor and pump are protecting me. We didn't choose to have type 1 diabetes, but we should be able to have access to life saving devices in order to manage it. I'm lucky to have an insurance plan that covers a large portion of the expenses and insulin pumps, but there are too many people who don't have them, and oftentimes, they are the ones who need these devices the most. I strongly urge you to cover continuous glucose monitors, especially along with insulin pumps, knowing that for us it means the difference between carrying a horrible burden and freedom or confidence, and literally for many, the difference between life and death. Thank you.

Josh Morse: Thank you. Next speaker, Michelle, I'm gonna butcher this, is it Realtorhizer? You're gonna pass? Thank you. Jen Mirahan. Okay. Thank you. Polly Shrek. If you could please tell us if you have any conflicts or if anybody funded your travel here today.

Polly Shrek: I'm representing myself.

Josh Morse: Okay. Thank you.

Polly Shrek: My name is Polly. It's a little awkward. I prepared something and it's still in my car. So, I tried to write a few notes here and there. I'm a mom first and foremost. I am also a cancer survivor. At age 29, I was diagnosed with

breast cancer. It was before I had type 1 diabetes, and doctors think that there is a connection with me receiving type 1 diabetes after my chemo and radiation, somehow my pancreas has failed me. So, anyways I was given a second chance at life and also a chance at being a mom. I'm now a single parent and just recently had to move in with my mom at age almost 40. So, kind of a slap in the face, but hey, I'm still alive, and I'm happy, and this has been a miracle for me. As far as type diabetes goes, I've only had it for about four years now. So, I'm still learning, and I was only able to use a pump, not ever a continuous glucose monitoring, but a pump when I was pregnant with my daughter. It was literally pretty much confiscated from me the day after my delivery. So, now I live with my mom and it was suggested by my doctors that I don't live alone with my 2-year-old daughter. I have tried to teach her how to use my phone in order to call 911. I see the one minute card, but I'm going to keep talking. I'm just kidding. I feel like I have... well we all do have a very important message. My point is, like Jennifer, I don't remember your name, sorry. This is, for me, it is a matter of life or death. I woke up once to a 29, and I was by myself. Luckily I had some juice next to me, but it scares me. It's mind blowing to think that my daughter could wake up and be laying next to me and not have a mother. What would she do? So, I imagine a lot of you guys are parents. And I ask you to imagine trying to teach your daughter or your child at 2 years old how to use... or to show someone where your glucagon is, or how to dial 911 or emergency on the phone. Anyways, I see the stop card. Thank you for listening to our stories, and I hope and pray that you guys will do the right thing. Thank you.

Josh Morse: Thank you. Our final listed commenter in the room is Laura Keller.

Laura Keller: Hi. My name is Laura Keller, and I work for the American Diabetes Association, and I don't have any conflicts with any of the pharmaceutical companies. One, you have our comments. You know the ADA is the gold standard of care for diabetes in the country and often referred to in the world, and we do recommend continuous glucose monitoring, and you've received that information. One of the things I want you to think about when you're weighing the cost of continuous glucose monitoring, because obviously that's what you're here to do is to look at the cost and the effectiveness. You know the data. You know that it limits severe hypoglycemia. You've heard from people that it impacts their lives. What I want you to remember is that in the cost, the State, Washington State is saving money on hospitalizations and people being able to go to work. There's a study that came out in January, which you probably haven't seen, that shows that students with diabetes have less absences from school. So, they miss less days of school. When kids go to school, their academically achieving. When they're academically achieving, those

schools and those teachers do better on those standardized tests, and then they get graded better and get more money for education, our education rises, and our workforce increases in their ability to be productive citizens. From a discrimination standpoint, it ends discrimination, as well, against keeping kids away from playing sports or other activities in school. Often, diabetes can be a barrier, but also, in the workplace, there are a lot of people whose livelihood is driving a truck, and while you can have a commercial driver's license when you have diabetes, it is very hard to maintain that, and there are a lot of regulations. So, a lot of people will refuse to go on insulin, because they're afraid of losing their livelihood or their job. Continuous glucose monitoring is overcoming that. They are able to keep their livelihood, then they don't go on unemployment for the State. Then, their health is better, their family is provided for, and the State saves money economically, because people are working. So, I want you to think about the economic cost of continuous glucose monitoring that there's a broader picture than just the real-time cost that the State might pay because there are benefits that will outweigh that. Thank you, so much.

Gregory Brown: So that covers the people that signed up ahead of time, and the signup here. Is there anybody else here that wished to speak? Are we at our 40 minutes? Anybody on the phone that wished to speak? We are unmuted, correct?

Female: We are.

Gregory Brown: Okay, not hearing any, we appreciate those of you that presented and those of you that passed so we can stay on time. Okay. So, we are, actually I will just take a second. I need to introduce Dr. Brent Wisse. He's an endocrinologist at the University of Washington. He is our expert on our committee for this topic, and Dr Wisse, would you like to take a minute just to introduce yourself and your practice?

Brent Wisse: Yeah. Hi. I'm Brent Wisse. I've been an endocrinologist at the University of Washington, since 1999. I've been based primarily at Harborview for my diabetes practice, and I'm the director of the inpatient glycemic control team there. So, I've been involved in all aspects of diabetes care in the inpatient and outpatient side for some time now.

Gregory Brown: And, I'm sorry, any conflicts to report?

Brent Wisse: I have no conflicts to report.

Gregory Brown: Thank you. So, I believe we are ready for our evidence report.

Andrea Skelly: Hi. I'm Andrea Skelly from Aggregate Analytics. I would like to first take some time to acknowledge all of my colleagues who contributed to this report and thank you for the opportunity to present this afternoon.

As you've already heard from Dr. Lessler, this is an updated report. Let's see. I guess we need to go to the next slide. There we go. This is an update to a 2011 report, which focused on any type of glucose monitoring in individuals less than 18 years old, and as you already know, the updated report includes a broader population, and as you've heard from many sources, there have been a number of technological advances and improvements in glucose monitoring, continuous glucose monitoring technology, and there has been more widespread use in the technology. I want to clarify that this report does not include evaluation of insulin delivery systems. So, pumps versus multiple daily injections are not part of the scope of this report.

In terms of background, you've probably already heard a fair amount about the background. It's a serious condition. There are three major types that are being considered in the report, type 1, type 2, and gestational diabetes, those who are pregnant with either preexisting type 1 or type 2 diabetes. In terms of complications, again, as you are all familiar with, there are chronic longterm complications that increase with the duration of diabetes and also with, if the individual is in poor control. These include cardiac and vascular complications, macrovascular complications, as well as microvascular complications, such as neuropathy, nephropathy, and retinopathy. There are also other increased risks for infection and other problems. As you have heard many times now, hypoglycemia is important, and it's a clinically important concern. It is more common in children than adults, because they may be unaware of their hypoglycemic state. Hypoglycemia can damage the brain, lead to seizures, coma, and death, and severe hypoglycemic events, while they are rare, they do increase with age and are more commonly found in type 1 diabetes. Diabetic ketoacidosis is another type of complication relating to severe hyperglycemia, and it can lead to the hospitalization in children with type 1 diabetes, and it can lead to coma and death.

As you know, diabetes duration is associated with chronic complications, and therefore, individuals who are younger have the most to gain from maintaining good glycemic control, because they have the longest to live with that, and yet, they have some of the greatest challenges. Any of you who have teenagers or children getting them to eat when you want, what you want, and how you want is a little bit different situation. The goal, overall, is to have the individual achieve or maintain glucose and A1c levels

as close to normal, as possible, while minimizing the risk of severe hypoglycemia. An intensive management type control is the standard of care for diabetes management, and glucose monitoring is a very important and integral part of that management. It provides important information for decision making, as well as assisting with and identifying hypoglycemic, and it provides peace of mind for caregivers for both older and younger individuals.

The standard of care, since 1975, has been the fingerstick self-monitor of blood glucose. I'm sure you're all familiar with it. Capillary blood is taken and read through a bonnet or providing a snapshot of where the blood glucose level is at any given time. General recommendation is that it be done four times a day, but depending on the individual, more frequently may be required. There are some barriers to that. You have to stick your finger with a lancet, and sometimes that's difficult to get blood, so sore fingers and difficulty getting samples. Those are more issues related to the devices to obtain the blood sample, not the meters themselves.

There are two general types of continuous glucose monitors that we will be discussing. Dr. Lessler described them briefly in his comments. We will be referring to the ones that have been historically used called traditional... we're going to call those traditional realtime glucose monitors, and the traditional realtime glucose monitors involve, as you already know, a sensor, a transmitter, and a receiver. The sensor is subcutaneously placed and allows for a sound plate of interstitial glucose levels, and it's connected to a transmitter, and if you look at the lower picture, you can see a picture, a stylized picture of the transmitter and the sensor. The glucose data is sent continuously to the receiver and, as you've heard, you can get it in your smartphone or your smartwatch and evaluate the values that you have been experiencing over a period of time, as well as realtime changes and the direction. Is it going up? Is it going down? How rapidly is it going up or down? As you've learned, there are thresholds for high glucose or low glucose that can be set, and they may be used with an insulin pump. You may see that referred to as sensor augmented pump therapy. All devices require fingerstick blood glucose for calibration at this point in time.

By contrast, the flash glucose monitoring, although it's classified as continuous glucose monitoring, is a little bit different. There are some important differences to keep in mind. First of all, yes. It does use a sensor. FDA requires only for upper arm use at the time, and it does sample interstitial glucose, not blood glucose. And it does store the data for eight hours. The sensors must be scanned by a separate reader, and you can see that the lower panel... you see the sensor implanted... or a

sensor attached, and then a scanner that is there. The data are not continuously made aware of to the patient. The patient is not immediately aware of them. The patient must actively scan the device in order to get information on levels, trends, and any alert messages. The FDA has only approved this device for those over 18 years old and the device is not necessarily... you do not have to do a fingerstick for calibration or treatment decisions with this device. Again, one of the major issues to keep in mind is that there are no automatic alerts with this system. The patient has to actively scan the sensor in order to get that information.

As you've heard, there are a number of advances in continuous glucose monitoring technology. One of the more important ones is the increase in accuracy and precision compared to earlier devices. The timeliness of display is the display of alarms, both visual and audio, have improved over the years, as well, as has sensor durability, the ability to wear the sensors longer, and the decreased size of the sensors, as well. Some of the devices, traditional devices, still do require fingerstick for verification. Those are referred to as adjunctive devices. As you heard, therapeutic devices are considered a replacement for fingerstick blood glucose for treatment decisions. In other words, they're used as a primary system and not as an adjunct. The Dexcom 5G is approved for that use. The Medtronic MiniMed, which is connected to an insulin pump, as you've heard, uses the glucose monitoring data to administer basal insulin, as required. However, that device is formerly approved for decision making for treatment decisions. Self-monitoring blood glucose fingerstick is still required for calibration, and with both the flash glucose monitor and the traditional monitor, there are instances where it may be important to do a fingerstick, for instance, if the reading is not consistent with the symptoms someone is experiencing, or something is wrong with his [inaudible]. Patient education and support, as you've heard, is very important, as is adherence, in order to get the best use out of these devices. Again, the flash glucose monitor differs from the traditional glucose monitor, as we've discussed.

Mika Sinanan: I'm sorry. Mika Sinanan. Can I ask a question?

Andrea Skelly: Yes.

Mika Sinanan: How long does the sensor, once it's implanted, continue to work?

Andrea Skelly: I don't know how long it continues to work. I think the advice, depending on the manufacturer, they need to be replaced anywhere between three and seven days. The flash glucose monitor has been approved for sensory use up to ten days, I understand, by the FDA. It's used for longer, I think 14 days, in Europe.

Mika Sinanan: Thank you. And just to be crystal clear in my own mind, the flash device would not address the critical nighttime hypoglycemic episodes that we heard about from a number of patients? Is that right?

Andrea Skelly: Unless it were to be actively scanned at night.

Mika Sinanan: Unless they were awakened, they woke up and scanned it?

Andrea Skelly: That is my understanding. That is my understanding.

Mika Sinanan: Thank you.

Andrea Skelly: So, let's see. We're going backwards not forwards. We don't want to do that. So, you are already aware of the key questions for the report, as well as the general scope of the report. Any individual with diabetes, studies of those individuals were included. Any FDA approved device whether it's adjunctive or therapeutic was considered. Any studies with those devices were considered, as well as any devices that were integrated with pumps. Comparators you're already familiar with. As far as study design, we do focus on the highest quality studies, in other words, those that have the least potential for bias and those generally included a randomized control trial and crossover trial for the first three key questions. And the randomized control trial, because they do represent the lowest risk of bias, were the basis for the strength of evidence ratings provided in the report. Observational studies were included. We really actively sought to look for longitudinal studies that were able to correlate intermediate outcomes, such as hemoglobin A1c or other measures with longterm clinical outcomes, such as micro or macrovascular disease or other outcomes. We did also consider observational studies for safety, and for economic studies, only full economic studies were considered for inclusion.

Only full length publication published in English in peer reviewed journals were included. The FDA reports, such as the SSEDs were also included. We did not include meeting abstracts or proceedings. We updated the search relative to our previous search dates for the 2011 report related to children and 2012 AHRQ had a report that we used as a basis for the randomized control trials in adults and individuals with type 2 diabetes requiring insulin, and pregnant women. So, we updated the search from that.

The primary outcomes for clinical outcomes were micro and macrovascular disease, and then for among pregnant women, fetal outcome, cesarean section rates, and of course, maternal outcomes. The primary intermediate outcomes, for which we assessed strength of

evidence, were achieving a target A1c and maintaining a target A1c. We looked at both success, in other words, ability to meet a specific target, as well as the change in the mean from baseline. As per the previous report, a clinically meaningful change of 0.5% was considered a clinically-meaningful change. Secondary intermediate outcomes are in the full report, and they included hyperglycemia, ketoacidosis, and quality of life measures. We will not be discussing those in any length at this point, but they are in the full report. For safety, we looked at any device-related adverse events and mortality. For economic studies, the outcome is the incremental cost-effectiveness ratio or any other similar metric, such as cost savings per morbid event averted. From over 2900 citations, we retained 56 publications. You can see the breakdown here. A caveat to note for those of you who add this in your head to keep awake is that, it will not add up to the same number, because some publications included more than one patient population. They may have included children, as well as adults.

We included both parallel trials, randomized control trials, or what we may consider the traditional randomized control trial and crossover trials. In a traditional randomized control trial parallel trial, individuals are randomized to treatment A versus treatment B and intended to stay with those treatment groups throughout the study and analyzed as randomized. Crossover trials are a little bit different, in that patient populations are randomized to first treatment A versus treatment B, and then after a washout period, which theoretically does not allow for the carryover of effects, whether that's from a pharmaceutical or even a behavioral aspect. Then, individuals get the other set of treatments. They have some advantages and you can require a smaller patient population, because each individual is their own control; however, there are some unique sources of bias and crossover trials that need to be evaluated, as well. Metaanalysis is not well done by combining parallel trials and crossover trials. There really is not a good methodology. For this report, we did not do that, but we will show you data for both sets of trials. There, are, again, some unique biases that we also have explained in the appendices to these types of trials.

So, each individual study is given a risk of bias. That's only one component of the overall strength of evidence. The strength of evidence for a given outcome is across the body of evidence, and it's based on five domains. The first domain is the risk of bias, and many of the ideas that you see here should be familiar to those of you who have looked at randomized control trials. In addition to the risk of bias for trials, the consistency of the estimate. So, to the degree to which different studies appear to say the same thing, in terms of the effect estimates, the directness of the

outcome, is it related directly to patient health outcomes, the precision which relates to the degree of certainty around effects estimates, and then finally, publication or report bias. Those are the five domains. So, as part of the systematic review process, studies are assessed for risk of bias, and then combined with those other domains, an overall strength of evidence is given, as either high, moderate, low, or insufficient. Based on the confidence that we have with the effect estimate, reflects the true estimate if you were able to do the ideal study in lots of people.

So, we're going to turn to type 1 diabetes and look at the results. In persons under 18 years old there are two new RCTs that we added and five new observational studies in patients with type 1 diabetes. This is all new to this report. Most studies were industry funded. If we look first at individuals under 18 years old, and look at the parallel trials, the proportion of individuals achieving an A1c of less than 7% is given in this plot. And I realize it's a little bit small, but I believe you do have copies of the slides. I'd like to draw your attention to the first two columns. The first column gives the baseline A1c in the study, and then, the second column gives our estimate based on what the individual trials gave for the wear, the use, how compliant people were, whether it was 60% of the time or not. As you can see in the plot, at three months, there were a greater number of individuals who, in the continuous glucose monitoring group, who achieved success versus those in the self-monitoring group, but at six and twelve months, there were no clear differences between continuous glucose monitoring and self-monitoring. We considered the strength of evidence for that to be moderate. And at three months, it was considered to be low. If we take a look at the percentage of individuals achieving an absolute difference of 5%, we again see that more children in the continuous glucose monitoring group achieved success than individuals in the self-monitoring of blood glucose group. And at six months, there really was no clear difference with one trial showing a significantly greater number of individuals, but another trial not showing that. So, there is some heterogeneity here. Similar, the JDRF trial, which is the JDRF 2008 you see in your slide, they also indicated that significantly more individuals in a continuous glucose monitoring had a 10% decrease from baseline in their A1c.

If we take a look at the next slide, it has to do with the between-group differences in the mean A1c change from baseline. You can see that there is some heterogeneity across the studies, in addition to which you can see that the results for the three months, there is a small reduction favoring continuous glucose monitoring. So, the mean difference is -0.22% in the A1c. So, it's a small difference. The question is whether or not it's clinically meaningful. At six months, again, there was no clear difference in the

parallel RCTs; however, one of the crossover trials, [inaudible], did find that after six months of continuous glucose monitoring treatment, both times was given to individuals, there was an almost clinically meaningful difference in the change from baseline in A1c.

At 12 months, there was no difference. We considered the strength of evidence for that to be moderate. Again, you can see that one trial clearly shows that there was a statistically significant difference. The other trial does not.

We looked at the time spent in hypoglycemic range, and we can see that at both three months and six months, there were no differences. The strength of evidence was low. And this is at the range of what is now called a level one hypoglycemic range of less than 70 mg/dL. This is the minutes per day. If we take a look at time spent in a hypoglycemic range of less than 55 mg/dL, again, we see that there is no statistical difference in the trials that are represented here.

With regard to severe hypoglycemic events, there were no differences between self-monitoring and continuous glucose monitoring. This is likely due to the fact that the studies were underpowered to detect rare events. So, that's an important thing to remember.

John Bramhall: Can I just ask, just for clarification, how was it determined, the time of hypoglycemia with blood stick monitoring? What's the operational method for that?

Andrea Skelly: Some of the patients did have blinded continuous glucose monitoring, and some of them, I... it's... I have to be frank with you, it's a little bit unclear for some of the trials. Obviously, if you're doing a fingerstick, it's going to have fewer data points, and it's going to be more difficult to do this. I think some of the data were among individuals who had sort of a blinded continuous glucose monitoring. They were unable to use the information, but the data were collected.

John Bramhall: Okay. Thank you.

Andrea Skelly: So, severe hypoglycemic events are generally those that are related to a change in either physical or mental state and requiring third party assistance. It can, again, lead to coma. It can lead to seizures, but in any of the ways that it was measured in these trials, there were no statistical differences between the two treatment groups, but again, the studies were underpowered to detect these. Again, you can see that the continuous glucose monitoring group, if you look at the incidents where

we were able to evaluate and find incidents that yes, there was less incidents of severe hypoglycemic events in individuals who had the continuous glucose monitoring, but it wasn't statistically significant. Again, the studies were underpowered to detect this. I would like to also say that there were none of the newer devices represented in any of the trials that were included for children. There have not been trials in the newer devices for children.

We did not do strength of evidence on these outcomes. They are detailed more in your report, but we felt it important to indicate that in terms of adherence, if we look at extension studies to the randomized control trials, adherence was generally associated with greater reduction in the A1c levels. It is unclear, though, whether this would hold true in a comparative situation and in the figure six on the report, we attempted to, again, categorize studies where the adherence was at least 60% versus those that were not, and it was difficult to identify any clear patterns. With regard to quality of life and satisfaction, satisfaction was generally better among individual patients who had continuous glucose monitoring versus the self-monitoring, both in terms of the children's responses and also their parents. There was also increased satisfaction with increased use of continuous glucose monitoring. In general, there were no differences in quality of life measures between the two treatment groups, and that was among children or their parents, as a proxy.

So, we're going to now transition to adults with type 1 diabetes. Okay. So, in individuals, again, same plot format. We have baseline A1c. We have an estimate of whether or not adherence was at least 60%. Again, you can see that at three months, more adults achieved success in terms of hemoglobin A1c of less than 7% in the individual trials at three months. The pooled estimate is not statistically significant because there is a lot of heterogeneity. So, we don't want to put a lot of stock into the pooled estimate. The Beck 2017 does represent one of the newer devices, as you can see, although additional individuals... more individuals with continuous glucose monitoring did achieve the threshold. The effect size is much less than with the older device. I don't know why that is. Again, at six months, you can see that more adults did achieve success. The pooled risk difference was 23%, and at 12 months, again, there was one trial, again evidence that there were individuals who achieved success. The strength of evidence for all of these time periods was considered low.

If we look at other ways of looking at achieving success or specific A1c ranges, relative reduction of 10%. Again, we see a similar pattern that more achieved success with continuous glucose monitoring at three months and at six months. The same with an absolute reduction of at least

5% from baseline. You can see at both three months and six months there were more individuals who achieved success given those thresholds.

If we look at the mean change from baseline across trials, you see that there is a lot of heterogeneity. A lot of differences in the effect estimates. Again, the Beck 2017, which is the Diamond trial, you can see that the effect size estimate is certainly consistent with the other from the standpoint that the confidence intervals overlap and the pooled mean difference is consistent with the findings of the Beck trial. Same thing at six months. Again, it appears that traditional continuous glucose monitoring is associated with significant improvement in mean change in A1c from baseline. The strength of evidence was considered low. Again, at 12 months, we only have one trial. Here's where the flash continuous glucose monitoring had data. There was one randomized control trial that was considered at moderately high risk of bias, and the mean difference was not statistically significant, but it must be pointed out that this was a population where the individuals were under good control. Their A1c levels were already less than 7.

If we take a look at comparing the parallel trials and crossover trials, please bear in mind that this is an indirect comparison. And if we take a look at the parallel trials, again, the last follow-up, we just looked at the last follow-up for the parallel trials, you can see that again, there is a clinically and statistically significant decrease in hemoglobin A1c percent over whatever the final time period was. There were two sets of crossover trials, one which included... two of which included crossover, or treatment periods of at least six months followed by a washout period before the other set of treatments was provided, and then one which... two which used much shorter timeframes for treatment. If we look at the middle set of bars for the crossover trials where there was at least 26 weeks, six months of treatment, the findings appear to be similar to what we see with the parallel trials in terms of the mean difference in A1c being statistically and almost clinically significant. The two crossover trials for which there was a shorter time period do not appear to... do not show any statistically significant improvement from baseline in A1c. It should be noted that two of the trials were newer devices, the Gold trial, which is the Lind, and the Beck, which is the Diamond trial. And the newer trials for newer devices, the findings are not inconsistent with the findings from the older trials. One trial, the In Control trial, showed no statistical difference.

Mika Sinanan: Mika Sinanan. Could I ask a question?

Andrea Skelly: Yes.

- Mika Sinanan: The washout period. I understand the importance of not having one run into the other, but what do they actually do during the washout period? They have to be measuring their blood glucose somehow, right?
- Andrea Skelly: Some of them did use a blinded continuous glucose monitoring again, and some of them, and then they were all still... they were... all of these were supposed to also be doing some form of blood glucose [inaudible].
- Mika Sinanan: So, they were self-monitoring continuously throughout? I mean, it had...
- Andrea Skelly: I'd have to go back and look at the individual trials to answer that, and we can certainly look at what the... some of them were not really good about telling us what happened during the washout period.
- Mika Sinanan: But it just sort of begs the question about what it means for a washout. A washout means you're not paying attention or collecting data during that period, but the patients are actually monitoring their blood glucose.
- Andrea Skelly: It still, yeah.
- Mika Sinanan: They have to be.
- Andrea Skelly: They're monitoring, yeah.
- Mika Sinanan: Right. So, it's not a washout from the therapeutic intervention. It's a washout from being observed?
- Andrea Skelly: I guess, yeah. That's one way to think of it, yes.
- Gregory Brown: And how long were those washout periods? Are they a range or?
- Andrea Skelly: I would have to look up... I think washout periods for the 2 six-month trials were, I think, 14 weeks.
- Gregory Brown: Okay.
- Andrea Skelly: For the shorter period trials, I'm going to have to have [inaudible].
- Gregory Brown: No. That's fine. I'm just getting a rough range, and...
- Andrea Skelly: And we can [inaudible].
- Gregory Brown: If I understand...

- Andrea Skelly: ...information too, about what happened during the washout period.
- Gregory Brown: Okay. And Dr. Wisse, hemoglobin A1c change, you expect, in a month, a 30-day period?
- Brent Wisse: A change, you can see it, but it's, you know, it's over a three-month that the hemoglobin A1c is measured. So, within one month, the change could be relatively small. It is biased towards the more recent timeframe, but you're certainly not expecting a full change after one month.
- Gregory Brown: So, a 14-week washout would cover that period, though? Okay.
- Brent Wisse: Correct.
- Gregory Brown: Thank you.
- Andrea Skelly: Okay. So, again, we looked at time spent in a hypoglycemic range of less than 70 mg/dL. The pooled estimate suggests that there was less time spent in this range, in terms of minutes per day, 21 minutes less per day in the individuals who had continuous glucose monitoring compared to self-monitoring of blood glucose. In the crossover trials, each trial... many of these trials measured things differently. So, it was not always possible to reconcile the units of measure, in terms of minutes per day or hours per day. One of the crossover trials, the one that had the 16-week treatment period, found that there was a 1.1 hour/day difference favoring continuous glucose monitoring in terms of less time spent in this hypoglycemic range. For the flash glucose monitoring, there was significantly less time spent in this range, 1.24 hours per day. They give a standard error, not standard deviations, and that's kind of a fairly large standard error. The bottom line is that it appears that continuous glucose monitoring, both at three months and six months appears to result in less time in this hypoglycemic range in adults.

With regard to the hypoglycemic range of the lower range of 55 mg/dL, at three months, we see that again there is a statistically significant decrease in the amount of time spent in that range. At six months, the results failed to reach statistical significance. I would point out that the Beck 2017, again, is the newer device, and it was not significant and was bordering on not significant at the three-month period. For the flash continuous glucose monitoring, again, there was a statistically significant decrease in the hours per day spent in this range.

If we look again at hypoglycemic events in general, again, studies were underpowered to detect those events. So, there were no statistical

differences between trials. Unfortunately, again, because they were underpowered, that lack of statistical significance needs to be considered in light of that. On three crossover trials, only one small trial reported significantly fewer severe hypoglycemic events with continuous glucose monitoring. The flash continuous glucose monitoring, there were two patients in one group and three patients in the self-monitoring group. Again, not enough power to detect a difference.

If we look at some of the other outcomes, again, for which we did not do strength of evidence, again, single arm extension case series, basically, of the trials suggests that there is greater adherence, there are better A1c levels, and again, the comparative evidence is not clear. In terms of satisfaction and quality of life, two RCTs, including one of a newer device, increased patient satisfaction is higher with continuous glucose monitoring than with self-monitoring, and with increased use, patients become more satisfied. The results for quality of life varied substantially across different measures and is very difficult to draw any conclusions across those measures.

We'll move now to mixed populations. Mixed populations in this context means patients... they included patients who were children, as well as adults. In most studies, it was about 50/50, adults 50% children. Most studies, again, were industry funded and there two observational studies that were not.

Looking at the success in terms of achieving an A1c of less than 7%. We see that at three months, significantly more patients with continuous glucose monitoring did achieve the target with a risk difference of 19%. There were no differences, however, at six months. What's unclear to me is to what extent the mixing of the populations of the children and the adults may influence that. The types of technology that were used, the study protocols. It's kind of hard to know why these results are a little bit different than what we've seen in children separately and adults separately.

Mika Sinanan: Mika Sinanan. Can I ask you question about that? Looking at the dates of those studies, 2008, 2009. So, that represents technology that was developed and implemented at least two years earlier, right, to collect the data. We heard earlier that the technology is moving rapidly, improving. So, could you comment on that, as a risk factor for interpreting this information? I mean, is it relevant to the current technology?

Andrea Skelly: It is certainly possible that the technology difference may impact these results; however, if we go back to the adults and what we saw in the adults

the newer devices, the results were not totally dissimilar to what the older devices were, and although these are older studies, many of them are considered pivotal studies and are still used as the basis for clinical guidelines and other things. So, technology may not any longer be used, and that may definitely impact the results.

Mika Sinanan: Thank you.

Andrea Skelly: But there may be other factors, as well. If we take a look at the between group differences in terms of change from baseline, again, we have at three months, across the parallel trials, we see that there are small reductions in A1c favoring continuous glucose monitoring. At six months, across four parallel trials, again, a small improvement. The question is, is this clinically meaningful? And in one crossover trial, Battelino, there was a small, approaching clinically significant improvement in A1c, and again, it's unclear whether some of the smaller differences are clinically important.

If we looked again at time spent in hypoglycemia, again, these are older devices, and here's where it may definitely have an impact, we see that there are no statistical differences at three months. There was less time in this range noted when we pooled across studies at six months.

If we take a look at time spent in hypoglycemic range of less than 55 mg/dL, we see that there are no statistical differences at either three or six months, and if we take a look again at severe hypoglycemic events, again, it's unlikely that studies were powered sufficiently to detect a difference between treatments.

When we look at severe hypoglycemic events that were associated with seizure, coma, or loss of consciousness in the parallel trials, again, we didn't see any difference. One trial, the Switch trial, did show that in terms of the times when patients were using continuous glucose monitoring there were fewer events than during the times when the focus was on the self-monitoring of blood glucose, but again, the power may not have been there to decline a statistical difference.

Mixed populations, there really wasn't as much data, in terms of adherence, but greater adherence was associated with improved A1c. Quality of life, there were none of the trials, which included information on quality of life. I would point out, as was suggested earlier, that none of these trials in the mixed populations were of newer devices.

If we look at patients with type 2 diabetes, there were five RCTs, four of which were industry sponsored, and one observational study. Not all trials, by the way, contributed to all outcomes. Some trials reported some things, other trials reported other things. The only trial that reported achieving specific thresholds for success was the Beck trial, which was a newer device, and there were no clear differences at three months, and no difference at six months, in terms of patients achieving an A1c of less than 7%; however, if you take the metric of an absolute reduction of at least 5% from baseline, more continuous glucose monitoring patients achieved this threshold when they used continuous glucose monitoring than those who had self-monitoring at those time points.

Between group differences, again, are consistent from a standpoint that at three months and six months, there was statistically significant reduction in the A1c from baseline with the use of continuous glucose monitoring. Here, we do have a representation of a trial with a new device, the Beck 2017, and again, the effect estimate is not inconsistent with the effect estimates for the other trials, nor is the pooled estimate, which is very consistent with the Beck trial. At nine months and twelve months, there was only one fairly small trial available, and it was not considered to provide sufficient evidence to draw a conclusions.

For the flash continuous glucose monitoring, this was, again, another new device. The adjusted mean difference at six months was not statistically significant; however, we can consider the results from this trial to be insufficient. If we look at times in the hypoglycemic ranges of less than 70 mg/dL, and less than 50 mg/dL, we see that we don't have the data. We can tell you what page in the report that it's found in, but there were no differences between continuous glucose monitoring and self-monitoring in terms of minutes per day, percent of readings in a given range, or percent of time spent in either range across two trials at three months for hypoglycemia and six months at a level of less than 50 mg/dL or for hypoglycemia less than 70 mg/dL. The flash continuous glucose monitoring device did show statistically significant decrease in time spent in both of these ranges, favoring the flash continuous glucose monitoring, but the strength of evidence was, again, considered insufficient, primarily because this was downgraded for risk of bias, as well as a single study and lack of precision.

If we take a look at severe hypoglycemia, it was less well reported in these studies than it was in the patients with type 1 diabetes. Again, I think conclusions are very difficult, because the studies were underpowered to define a difference between trials, and again, it was poorly reported. Two trials did not define what they meant by severe hypoglycemia, and one

reported no events over three months. We don't know whether... what group that belongs to, or both groups. A second reported the frequency in both was negligible with no serious events. So, the reporting for severe hypoglycemia in these trials was very poor.

In terms of the other outcomes we've been discussing, greater sensor use was, again, associated with better reduction in A1c to twelve months in one trial. In terms of satisfaction usage was associated with improved satisfaction. In both the trials of continuous glucose monitoring as a traditional continuous glucose monitoring, as well as the flash continuous glucose monitoring. There were no statistical differences in any of the quality of life measures in one trial in a newer device, one trial of an older device or, in most measures for the flash glucose monitor.

Turning our attention, now, to diabetes in pregnancy, in terms of individuals with preexisting type 1 diabetes in pregnancy, there were two trials and three observational studies. Again, most were industry funded. Preexisting type 2 diabetes, there was one small RCT. In gestational diabetes, there was also one small RCT.

Statistically significant clinically important differences were found following use of continuous glucose monitoring for cesarean section rates, as well as newborn admission to neonatal intensive care units. Satisfaction, there were favorable ratings among individuals who used the continuous glucose monitoring, but there were no statistical differences in quality of life measures. So, these were the primary findings in individuals with preexisting type 1 diabetes who became pregnant.

There were no statistically significant differences in any of the other measures that we looked at, and the strength of evidence and the number of trials are based on who reported what measure. It's likely that some of these outcomes, again, represent rare events, and it was not... there was not enough statistical power to detect a difference between the devices.

If we take a look at individuals who had preexisting type 2 diabetes prior to pregnancy, there was no difference in any of the outcomes measured, but there was only small trial of 31 women. So, at least some of those lack of statistical differences is probably due to poor sample size, low sample size, and because of the type of trial, single trial, lack of precision, we considered the strength of evidence to be insufficient.

Similarly with gestational diabetes. We had another trial, a little bit bigger trial, but again, there were no statistical differences in any of the outcomes listed here. Again, some of these may be considered to be maybe rare

events. So, the studies were likely underpowered to detect differences in all those outcomes.

I'm going to preface the section on safety with a bit of a disclaimer, and that is that trials reported safety in very different ways at very different times and with very different definitions. So, drawing from conclusions across studies on many of the safety events is very difficult.

Gregory Brown: Actually, I was just going to interrupt for a second. We're kind of at our normally scheduled break.

Andrea Skelly: Okay.

Gregory Brown: So, my question is, and to the committee is, do we want to continue, can we focus on just the higher strength evidence for this part? How would we like to proceed?

Mika Sinanan: Let's take the break now, and when we come back, if you could parse your slides and just choose the significant evidence. Very often, you have said, but we can't trust this data or it's insufficient. So, my thinking is, just take that out. There's no point in even looking at it from your presentation. It's nice to have it here.

Andrea Skelly: Okay.

Mika Sinanan: But let's focus on those which can help us make a decision, not the insufficient evidence.

Andrea Skelly: Okay.

Gregory Brown: Does the rest of the committee agree with that? Okay. Then we have ten minutes, please.

I think we're ready to resume. We have our speaker ready. Thank you.

Andrea Skelly: Okay. So, we picked up, when we last left our heroes and heroines, we were talking about safety. Again, I would like to say that there was substantial variation in the types of adverse events that were reported, their definitions, how they were classified, when they were evaluated, and again, definitive conclusions, I think, are going to be very difficult. There were no device-related deaths. So, that's an easy one to come to a conclusion about. There is limited data on newer devices in terms of safety. So, I'm going to breeze through these slides at the suggestion that we cut it... quicken things up here a little bit.

In terms of things that led to discontinuation, in terms... most adverse events, most all of them relate to sensor and skin related reactions. That's the bottom line. Some of the older devices, some of the concerns related to frequency of alarms and types of alarms. The new technology seems to have addressed a lot of that. So, what we're left with is, again, sort of a hodgepodge of things. Everything is low strength of evidence in terms of the types of things that led to discontinuation of devices, whether it's a flash continuous glucose monitoring or a traditional continuous glucose monitoring. The flash continuous glucose monitoring studies did not do a good job of reporting how they defined severe adverse events leading to discontinuation or symptoms that have the same names for adverse events. So, all of the flash continuous glucose monitoring, we considered insufficient. All of the trials that looked at other adverse events, we considered to be low strength of evidence. So, again, you can see sensor issues, allergic reaction to sensors in the one newer device, two trials of newer devices, couldn't upload the data was one of the issues, as well. It's interesting to note that in observational studies, 61% and 44% respectively, and two studies had similar reasons related to the above for discontinuing the use. If we take a look at serious device-related adverse events again. Most of them relate to skin reactions. There was one diabetes hospitalization, one trial that reported that for hospitalization for diabetic ketoacidosis, again, fairly rare, but it did happen. The newer devices, again, only two trials, one of them described retinal detachment as a device-related event. I'm not sure exactly how, but they did. Again, conclusions of the serious device-related events were relatively rare and sample size may have been too small to detect some of the most severe ones. Strength of evidence was low.

In terms of technical and mechanical problems, these were very poorly reported. The frequency varied, and it depends on how you classify device-related event. One said, oh, we just had a device issue without any further ado. So, again, the strength of evidence was low. The definitions, again, reporting of technical or mechanical issues was varied and not well reported across trials. Again, you can see that there is a broad range of nonserious device-related events. Again, most of them relate to either the sensor or insulin infusion site of skin related adverse events. That was most of the problems. Newer devices, again, one study reported 3% of individuals experienced skin-related problems. One cohort study found 36% of individuals had skin related problems. Again, nonserious related events were not uncommon. They were fairly common. We felt the strength of evidence was low, again, for the flash continuous glucose monitoring, because of the poor reporting. We were not able to draw any definitive conclusions.

In terms of differential efficacy and harms, changing, again, we have an insufficient... we really don't have enough data to define whether or not there are special populations which might do better with devices or not. There is one study, the Beck trial, in type 2 diabetics, which suggests that maybe the degree of hypoglycemic unawareness may be a factor, but again, we really are not able to draw conclusions.

If we look at the economic studies, there are five economic studies total that we reported on. The first one is done in Canada and represents the data from the Diamond trial. All of the studies, if you have a willingness to [inaudible] Dr. Lessler's slide of less than \$100,000 per QALY, things are considered cost-effective. This study by Chaugule, a Canadian trial, all of the studies used a lifetime horizon for their modeling of cost-effectiveness, and it's unclear whether or not that is appropriate, given that we only have randomized trial data up to 12 months. Some of the data that are used for modeling, complications and other things, may be data that may not represent current state of diabetes care. Both of these trials were industry funded. The other was from Sweden, again, using a lifetime horizon and was considered cost-effective by the authors for the treatment of type 1 diabetes.

There were two U.S. studies, again, both using older devices. The first study by Huang in 2010 was reasonably well done, but they found a wide confidence interval around the cost-effectiveness depending on what types of modeling assumptions they evaluated. Again, they used a long lifetime horizon. There were high baseline utilities. We won't get into that. It's unclear if the models for micro and macrovascular complications reflect current care. That was not industry funded. Then, there was one by McQueen, also in the U.S. Again, they suggest that cost-effectiveness at a willingness to pay \$100.00 per QALY may be true. In this study, the ICER based cost-effectiveness ratio really varied substantially based on their model assumptions and probabilities from different populations.

If we take a look at type 2 diabetes, there was one study, and it indicates that continuous glucose monitoring would be cost-effective, very low quality, \$8800/QALY, but they didn't really give us much information, in terms of sensitivity analysis and a probabilistic cost-effectiveness analysis suggests that 70% of the time willingness to pay of less than \$100,000 per QALY, it would be cost-effective, but this is based on one small trial, and again, a lifetime time horizon using an older device. It is unclear, again, if some of the inputs for the modeling reflect current standards of care. This was funded by Dexcom.

- John Bramhall: I know we're short on time, but can you just explain that cost-effectiveness again for me. I'm not sure that I understand it. The quality adjusted life year. So, like if I... so on the previous, this slide here, what is it saying? It's saying that if it costs \$8898/year to provide the service to one patient...
- Gregory Brown: No. So...
- John Bramhall: It's not saying that? It's saying something else?
- Gregory Brown: Let me take a quick stab, John. So, if you had a 10% quality in life over ten years, that would be one quality adjusted life year, okay? And then if the cost of treatment over that ten year period was \$100,000, that would cost you \$100,000 per quality adjusted life year. So, if you had an improvement in quality of life of 20% over five years, that would be one quality adjusted life year. I guess what I'm trying to understand is, I thought you had looked at quality of life in your outcomes, and you didn't find any differences in quality of life in any of your measures. So, if you didn't find any differences in quality of life, how can...
- Andrea Skelly: How can there be a...
- Gregory Brown: ...how can there be a quality adjusted life year here. So, I guess what I'm asking is, is if the quality adjusted life year is monitoring improved control, which improves quality of life, that's great, but four times a day fingerstick is the same potential quality adjusted life year improvement.
- Seth Schwartz: Can I say something? I think... quality of life is not the only outcome here, right? So, it's also duration of life. So, if you're reducing the events, if you're reducing hypoglycemic deaths, and you're reducing microvascular complications and all that other stuff, that could have an impact on quality of life, as well, even if the quality of life is not different, but that's super speculative, and maybe that's where some of the huge variability comes with is those are rare events, and they are... and it's uncertain to what degree this monitoring is effecting it.
- Andrea Skelly: Economic modeling is a whole science unto itself, and it's not just, as Dr. Schwartz was saying, it's not just quality of life, and there are different ways of measuring quality of life. In economic studies, these are cost utility studies. What they're trying to do is measure how much quality of life you will have given a specific state, and they call those utilities. The utilities that they may use in the economic modeling for these studies may be very different than what they use in the studies, the randomized control trials that we are reporting. The idea is that you take a look at the difference in cost over the difference in benefit, however, benefit is measured. So,

that's what the ICER is, the difference in cost over the difference in benefit in many respects. Then, benefit is measured in various different ways. It depends on what utilities they've used. I know there have been editorials about some of these studies not using the right utilities for this disease. Some of them are disease specific. Some of them are very generic, like, the SF36 can be reduced to a utility by means of transformation. It's different than the [inaudible] 5D. So, there's a lot of moving pieces here. It's hard to give you a specific answer, as to why quality of life were no differences here and we're seeing a difference answer for the quality of life here. And you're right. For the quality adjusted life year, it's okay, over one year, you know, how much does it cost to buy one additional life year, specific quality of life. Economic stuff is fun.

Gregory Brown: I think I'm going to take a Chair's prerogative, since we're over time, we have nice summary slides. So, summarizing what we've already covered.

Andrea Skelly: Yes.

Gregory Brown: So, let's open it to questions, then. That way we can... if there's a question about the summary slides, we can do that. So, I do have... my first question is, are these efficacy trials or effectiveness trials, in general? Do you have a sense or?

Andrea Skelly: The way we interpreted them, they are efficacy trials. So, those trials are considered efficacy trials. Effectiveness is generally measured using observational studies.

Gregory Brown: Okay. So, that means they are done under ideal situations.

Andrea Skelly: Presumably, yes.

Gregory Brown: Okay. So...

Andrea Skelly: So, they're not... these are not pragmatic trials, although there is one that you could maybe argue was more pragmatic.

Gregory Brown: And so, one recurring theme, I thought I saw, was that early on, there was a difference, whereas out at six months or a year, there was no difference between the groups. Is that a recurring theme there?

Andrea Skelly: It is. That's true for children.

Gregory Brown: Okay.

Andrea Skelly: With the adults, I think, maybe if we go to the summary slide, you can see that, that it does persist up to 12 months, in a purely adult population for both the success, as well as the mean A1c. This is for the traditional glucose monitoring, not the flash. The same is true for the parallel trials, as well as the crossover trials. The crossover trials are a little bit hard to grapple with, because you've got six months of treatment, washout period, six months of treatment with the other group. So, that's really sort of a six month thing versus a twelve month thing. So, I think that it's fair to say that at three months, six months, and twelve months, you do have some evidence in terms of the A1c outcomes of efficacy. At 12 months, your data are getting more sparse. You only have one trial that's involved. That's why the strength of evidence is considered low. Does that answer your question?

Gregory Brown: Absolutely. Thank you.

Andrea Skelly: Okay.

Seth Schwartz: This is Seth. We had talked about the correlation between outcomes and date of study in the adult population, but we didn't talk about it in kids, and I was wondering if you saw any trend towards differences based on when the trials were done, because we overall did not find a difference in kids, but was there any trend towards temporal differences?

Andrea Skelly: No. If you want to go back to a slide to look at that, I'm happy to do that.

Gregory Brown: I thought you said that none of the trials with children had the current technology.

Andrea Skelly: That's correct. None of them used the current technology.

Gregory Brown: Okay.

Andrea Skelly: Now, that I took the question to mean newer studies...

Seth Schwartz: I did, but that was the marker for technologies.

Andrea Skelly: Okay. Alright. Yeah. There was some heterogeneity, even with study time, yeah.

Mika Sinanan: Mika Sinanan. I am struggling with how to use the strength of evidence that you've provided.

Andrea Skelly: Okay.

Mika Sinanan: That's insufficient, doesn't push me in either direction. I can't use that as the basis for making a recommendation. Is that the way you think about it?

Andrea Skelly: The way I think about it is that there are not enough data for me, as, sitting from my perspective, to draw a firm conclusion. Now, you, as a clinician, may have a different perspective on that, but what I'm saying is that my confidence in the effects that I'm seeing is very low. I don't really have any confidence in what I'm seeing when I say something is insufficient.

Mika Sinanan: So, I think you said the same thing that I said, which is that a strength of evidence that is insufficient does not allow one to draw a conclusion in either direction on the basis of the data that's presented.

Andrea Skelly: Yes. Put that way, yes.

Mika Sinanan: Okay. And then low, how would you, how do you think about low strength of evidence?

Andrea Skelly: Low, I take to mean I have some confidence. There is some evidence, but it's a low level of confidence in that, if there are future trials that come along, the change may be very different than the results that we see here. So, my confidence is mitigated by the fact that maybe there are not enough trials. Maybe they're poorly done, but the effect estimate may change in the future if newer trials with newer devices with whatever come along. So, moderate then to continue the thread is, I mean, I have moderate confidence that this is pretty close to what the effect size will be. High confidence would mean, I'm pretty darn certain, although as certain as you can be. You can't really always be certain, but I have high confidence that newer studies are not going to disprove this particular outcome's effect size.

Mika Sinanan: Thank you.

Tony Yen: This is Tony Yen. Can you help me understand some of the studies a little bit better?

Andrea Skelly: Sure.

Tony Yen: It seems like the two U.S. studies are the Beck Diamond trial in 2017 and then the 2015 trial by New. Am I correct?

Andrea Skelly: Okay. So, the two Beck trials, there's one in type 1 diabetics, one in type 2 diabetics, and those both use newer devices. They use a Dexcom, I think, with a 550G software. Then, the Lind trial is the other... another one of the new device, and then, I think it's van Beers also used... that's one, that's one of the crossover trials. And then, the two freestyle Libre Bolander and Hack, those used newer devices. Those are the only trials that used newer devices. They were only in adults. There was nothing in the mixed populations. There was nothing in the children, and if you want, Erica has a list of what devices are used in what trials if that's of any interest or help. Most of these devices, many of them are no longer marketed. Some of them are still used. Some of them are being phased out.

Tony Yen: So, specifically, I had a question for you. I guess I can refer to the exact study on slide 31. It's kind of underneath the three to four month study period. There's New 2015, it seems to be, intention to treat trial. Is that using a newer device, as well?

Andrea Skelly: No.

Tony Yen: I guess I'm not interpreting that correctly then.

Andrea Skelly: I think it's a newer study, but that doesn't mean it was a newer device that was used. You said slide?

Tony Yen: Okay. 31.

Andrea Skelly: 31. Okay. Yeah. The New trial, also the new trial, it was... they did have some individuals who had type 2 diabetes, but more than 80% of them had type 1. So, we have included it in type 1. That may partially explain, you know, if they have some differences in their outcome.

Tony Yen: Sure. The reason why I'm asking this question is, it seems like you know... I'm trying to kind of frame this with more recent technology is the bottom line. It seems like the later studies would incorporate the newer technologies?

Andrea Skelly: Or maybe there's a time lag between the time they collected the data and published it. What device was used in the New trial? If my memory serves me, it was not one of the newer devices. Freestyle Navigator, which I don't believe is any longer available.

Tony Yen: Okay. Thanks, but it appears that the strength of evidence for at least a Beck trial, at least what you've listed over here as insufficient?

Andrea Skelly: No, so if you can direct me to where you're looking. So, the beauty of having forest plots is that you can see not only the pooled estimates, but you can see the individual studies, as well, and that's why I pointed out the Beck trial, because it does use a newer device. There are a couple of slides in adults. In fact, here's one of them. Slide 31 is one of them. If you look at three to four months, you can see that the point estimate for the Beck trial is a mean difference of 0.5. And if you look... that's the very top set of point estimate and confidence intervals. Then at six months, follow the line down, it's the same for the Beck trial. So, you can see that at three to four months, there are some trials that do show an improvement. Other trials don't show as much of an improvement. One of them has a large variability there. So, in addition to the metaanalysis, which is the pooled estimate, you have the opportunity to look at the difference trials. So, the point estimate for Beck, which is a newer trial, if you look at the confidence intervals and the overlap and the pooled estimate, it's not... it doesn't look like it's a lot different. There's a lot of heterogeneity going on here, to be frank, but the Beck trial data is there. The same thing with the six months. It's consistent with the Hirsch trial actually, and the pooled estimate is there. Again, there is a lot of heterogeneity, but the bottom line is, all of them are showing that there is an improvement in the mean A1c at last follow-up in the patients who get continuous glucose monitoring. Does that help?

Tony Yen: Yes. Thanks.

Andrea Skelly: Okay. Yeah.

Gregory Brown: Other questions? We can certainly ask if we have them come up.

Carson Odegard: Yeah. I just have one. Could you rephrase that again about you can't do a metaanalysis on the crossover trials versus parallel trials, but you can get a pooled estimate. You can get a pooled value between the two or not?

Andrea Skelly: Not incorporating, well... so, this slide here, slide 32, we have the parallel trials up on top.

Carson Odegard: Right.

Andrea Skelly: And then, we have the crossover trials that had similar treatment time periods in the middle bar at six months, and then two crossover trials that had different treatment periods, but we don't have a final total pooled estimate across them, because it's subject to bias.

Carson Odegard: No. I understand.

Andrea Skelly: [inaudible] at that.

Carson Odegard: So, you are comparing the crossover with the crossover then?

Andrea Skelly: Yeah. So, the pooled estimates across two of the crossovers are there, and they are... even there we maybe stretched it a little bit. So, I prefer to think of it as sort of indirect comparisons, but the Lind is a new device.

Carson Odegard: Mm-hmm.

Andrea Skelly: The Gold trial, Diamond trial Beck is a new device. Then, the In Control trial, which was the van Beers, it didn't show a difference.

Carson Odegard: Okay.

Andrea Skelly: So, you know, if we make... if we ask the question do newer devices make a difference, I mean, it's hard to tell. I mean, you see where the data are, and you can draw your conclusions.

Carson Odegard: Okay. Thank you.

Mika Sinanan: Mika Sinanan. One last question for me, the quality adjusted life year, we heard, again, testimony from a number of patients who said they believed the device may have saved their life. Is that... would that ever be captured? Would that be a one or, for a young person 20? Or is it only in the modeling that is discounted?

Andrea Skelly: Well, that's a big question that doesn't have a simple answer. It depends on how, it depends on how they determine the utilities. For some measures...

Mika Sinanan: For these numbers here, if somebody says it saved my life, and obviously that's a belief and we don't know what the alternative is, and thank God there wasn't an alternative. We do know those occur. That type of event wouldn't necessarily be captured here in that modeling?

Andrea Skelly: It depends on the measure used to use the utility. I mean, it could. I mean, there are many different ways to measure utilities. Some of them would maybe potentially capture. Most of them are probably not going to capture directly in that same way, but many of them are on a scale of zero to one. And depending on, not only that single event, but other aspects to the questionnaire, they may say on a scale of zero to one, I am here. And

that may be one factor that goes into that, but it may not be the only factor.

Gregory Brown: I think I have to disagree with you. So, I agree with your earlier statement that all the utilities measure something differently.

Andrea Skelly: Yes.

Gregory Brown: And a one on an SF60 is different than a one on an EQ5D.

Andrea Skelly: Yeah.

Gregory Brown: But they're all zero for death. So, there's no...

Andrea Skelly: Yeah. They're all...

Gregory Brown: ...difference there.

Andrea Skelly: ...zero for death. Yes.

Gregory Brown: And so, to me, the modeling gets into how... what probability do they have of death from a hypoglycemic incident? So, yes. If that happened in a 20-year-old and life expectancy is 60, you've lost 60 quality adjusted life years or whatever the ratio is of their quality of life during that 60 year period. So, that's the problem with these cost utility analyses is, they're highly susceptible to the frequency of these rare events. So, if you change, like I say, a death from a hypoglycemic event in a young individual from 0.001% to 0.002%, it could still have a dramatic outcome on this, and that's why you have the sensitivity analyses and everything on the cost utility analysis. So, I think the answer is yes, it could dramatically affect it.

Andrea Skelly: It could if the measure was appropriate to that question, and that was my point is that it may not be.

Gregory Brown: Well, okay.

Female: I would just like to quickly point out that Table 51 in the report, if you'd like to look at what the effectiveness outcome components were, they're all listed there. They give the assumptions and then the various health states that they used. It was, like, myocardial infarction, stroke, retinopathy, various things.

John Bramhall: Bramhall. There's a number of people in the country who have, for a variety of reasons poorly controlled glucose levels or poorly controlled

A1c, however it's measured. Do you... and this may be more of a question for Dr. Wisse. I don't know. Is there any information that comes out of any of these studies that suggests that people who have poor glycemic control with traditional methods, let's call them that, improve when they're offered something more sophisticated, like, a smartphone graphic interface. Is there any information at all?

Andrea Skelly: Well, from our analysis, we did not go into depth, but if we go back to some of the slides. Let's go to adults, because that's where we have maybe more of the information. We did try to capture what the baseline A1c was. I didn't put it in here, did I? Yes. I did. Yeah. So, you can see that the baseline A1c from these trials is over 7. Most of them are hovering over 8, and that does not seem to have impacted what the mean A1c is. We're just looking at one outcome, but that's not a formal analysis.

John Bramhall: Right. So, my question really to myself is, if you take people... let's just say with a hypothetical baseline A1c of 8 or 9, and then they enter a study protocol and one assumes that now in a study protocol, there probably is going to be an improvement, just because they're in a study and being guided, but my question really is, is there any evidence that this modern technology that we're not faced with improves their behavior outside of a study. I know that's an almost impossible question to answer from studies, because that's what I'm postulating.

Andrea Skelly: Unfortunately, our report does not capture that type of information in terms of how does their behavior change? Do they eat differently? Do they... we did not capture that information. So, I really can't answer that. I mean, one could postulate, well maybe there is some Hawthorne effect there when you're being observed and you do things differently. Maybe that continues after the study, or maybe it doesn't. Or even in the real world, as we noted on a previous slide, patient support is very important to this. So, maybe that's part of it. It may not just be the technology, but part of it may be that you have support and how to use the technology and use the readings to affect your treatment, etc.

Gregory Brown: But I mean, both groups are being studied. So, they both should have the same Hawthorne effect.

Andrea Skelly: In theory.

Gregory Brown: And so, what this is saying is that if continuous glucose monitoring reduced it by one and a half points on hemoglobin A1c, then the control only reduced it by one, 'cuz the mean difference was 0.5, correct?

Andrea Skelly: Yeah. On average.

Gregory Brown: Yeah. So, whatever control reduced it by continuous glucose monitoring, reduced it by another half a point.

Andrea Skelly: Yeah.

Gregory Brown: Okay. On average?

Andrea Skelly: I did have some concluding remarks if you're up for them. Or not? I take that as a not.

Gregory Brown: I think we're gonna pass unless... we want some time to be able to discuss this, I think. Certainly, if they are appropriate when we come up with a question, otherwise, we won't make you stand up there while we're having our discussion.

Andrea Skelly: And by the way, we do have information on the washout periods of the crossover trials if you're interested.

Gregory Brown: Okay. Thank you.

Andrea Skelly: Thank you.

Gregory Brown: Questions?

Laurie Mischley: So, I have a question just about the adverse events. I mean, we saw testimony earlier today about how my life is so much easier and better now that I have this. And we also saw a slide that showed that these were... the effects were better when the patient actually used them. Which leads me to ask why aren't patients using them if they have them? Why aren't they using them? And I see this huge incongruence between the adverse events leading to discontinuation in the RCTs versus observational studies? I mean, an observational study, some of these numbers are 61, 44% discontinuation. Can somebody shed some light onto... I mean, I don't want to provide these for patients who then choose not to use them. So, is that getting better with the improved technology? Are we not hearing about issues people run into in real life that we don't see in clinical trials?

Gregory Brown: I think that's a question for our expert.

Brent Wisse: I think that's a great question, and it's a tough issue. In trials, it's always tricky. A few are randomized to something, your adherence with it will be

less than if it's something you choose for yourself. That being said, there definitely... there are patients that get it and respond to it and run with it, as we heard from some very eloquent testimonials, and there are patients that do not. It's certainly the prediction of who is not 100%. With the older devices, sometimes, I mean, what is hidden in there is that when you're still changing out that sensor for some of them, you know, every three days, you're still calibrating it. So, you're still poking your finger, you know, a number of times a day, and again, with the technology, that is improved. So, with the newer Dexcom models, you are only calibrating it twice a day whereas in the past, that could have been more. So, that part of it is getting better, but for some patients, that's still a barrier, right? Where it's... I'm changing out this set again. I have to poke my finger to tell the machine what my blood sugar is right now, and so there are people for whom that's no barrier, and there are some patients where that's a barrier. That actually was part of the flash, which wasn't... we didn't really cover that well, but I think it's important to note that the flash sensor is auto-calibrated. So, you do not have to tell it what the blood sugar is and for my patients that say no. I'm not going to poke my finger. I don't want to poke my finger, the flash system is really a revolution, because they wear it for ten days, 14 in Europe as already has been pointed out, but we got, we got a bit of a reduction here in the U.S. They don't have to calibrate. They never have to poke their finger, and it gets rid of a lot of that unexplained variability. So, there are going to be people, when they're randomly assigned to something, that don't do it. And there is somewhere the barriers from the calibration or from changing the sensors is still an issue. So, it does, it does exist, but again, as you heard in the patient testimonials, the patients that get it and respond to it would never want to be without. I mean, they... it is such a life-changing event for them.

Mika Sinanan: Can I just, Mika Sinanan, follow up on that. As you think about the next patient in the next clinic you have, are there criteria separate from what we have heard, as recommended criteria for inclusion that you use to make a recommendation that this patient ought to strongly consider to be on a pump? And are there people who you just discount it by age, by background, by other measures?

Brent Wisse: So, sensor, not pump, right, because we're talking about the sensors.

Mika Sinanan: Sensors.

Brent Wisse: No. There's no one I discount it, but there's lots of people where, you know, it's a really nuanced discussion. For me, the part that I always focus on is what frustrates patients and what frustrates providers and Dan lived through this and [inaudible] medicine clinic, is unexplained variability.

Like, somebody that comes in and they tell you, sometimes my blood sugar is 50, and sometimes it's 350, and I have no idea why, right? As a provider, that's pretty frustrating. As a patient that's incredibly frustrating, because you have really nothing to work with. You can say, alright. Well, take less insulin at this time and take more insulin at that time, but you really are just guessing, and that's actually what this continuous glucose monitoring is terrific for, for patients that use it, again, that qualifier, and for providers, in that it gives you those 24-hour profiles. It says, hey, look at this. At breakfast you had... you went to Cinnabon and your blood sugar is this. Right? So, you can actually start correlating changes with particular... with activity, with certain meals, with certain doses of insulin, with certain times of day where you just have so much more data to work with. Again, some patients respond very well to that, and you can make really dramatic changes. The other comment related to that, that also came up that I just wanted to make... as you said, multiple times, and I agree with, the quality of the evidence is low for a lot of these and, in fact, the studies in some ways, I think, haven't been great in the way they've performed it, because they sort of mixed outcomes. Sheila was asking about this. I thought it was important to tell everybody, you know, the... the big way of looking... or the way to think about this is, as you improve A1c, and you get lower and lower, you are going to run up against a threshold, right, where if you're having someone who is starting with a good A1c, 7, less than 7.5, something, and which included a lot of patients in those studies, actually. The likelihood that you're going to get a dramatic improvement in A1c from using continuous glucose monitoring goes down. You're not going to see that dramatic effect on A1c; however, those are the patients that tend to have improvements in the time spent in hypoglycemia and fewer severe hypoglycemic events, as you heard from some of the patient testimonials. So, that, you're going to lose some of that A1c effect, but you're going to see that reduction in hypoglycemia, because the lower you get, the A1c automatically you're going to buy that patient some hypoglycemic time. The opposite is true. The patient that John asked about, and there is some data on that, John, so I think there was a subset analysis. I want to say it was in Diamond. Somebody in the audience will correct me if I'm wrong, that looked at the patients that started with A1c's that were higher, and they did show a greater reduction in A1c. Again, that's something that's relatively predictable, and someone that uses it in my own clinical experience also, the patients that start with an A1c over 9 that buy into this and use this will have much greater reductions in A1c, but that's something where... that's really an A1c, but for those patients, if you're looking... if those are included in the group and you're looking at time spent in hypoglycemia, well for a lot of the patients that goes from zero minutes to zero minutes, right? Or it may go from zero minutes and go up, because now their A1c is improving. And so, mixing those... the

hypoglycemic outcomes and indications in the A1c outcomes and indications actually washes out the power and washes out the significance for a lot of these studies.

Mika Sinanan: Can I ask a follow-up question then? Thank you. In other areas, I work with a lot of patients with inflammatory bowel disease, and the movement has been away from the sulfasalazine, steroids, and then those failures moving to biology therapy to more and more moving directly to biologic therapy, as a goal of reducing morbidity and delaying surgical therapy. The recommendations that Dr. Lessler provided include failure to achieve by standard measures for every one of them being an indication. Are you, in your mind, as you think about the evolution of this technology and some of the comments from the vendors, are we moving to a stage where continuous glucose monitoring is going to be applied earlier and earlier to therapy? Or, and maybe as firstline therapy, as opposed to rescue or an intervention for those who have failed more traditional measures?

Brent Wisse: I think that likely will happen. So, I think the quality of the data that you can get from point of care from self-monitoring, is always going to be limited, and you are always going to have better quality of data from continuous glucose monitoring. I mean, there's a lot of nuances that go into that. There are issues with measuring from interstitial fluid. Dan mentioned there is a lag time, in terms of that response, if the blood sugar is changing rapidly, but there is also a lot of problems with self-monitoring, especially now that a lot of plans are covering the cheapest strips, and the cheapest strips are the lowest quality. Some of them are really down to almost random number generators, in terms of what's happening with them. So, that's also not... it's not, like, that should be a gold standard, because it's a really... it's not gold you would want to make jewelry out of. So, it's something where you're kind of comparing it against another choice that isn't great. That being said, I certainly have patients, type 2 and type 1, especially newer diagnosed insured that have access to good meters and good monitoring where they get it, and their lifestyle isn't crazy complicated, and they're able to match the insulin doses to what they are doing, and they do great with self-monitoring and with multiple daily injections. For them, I say, well, you know, there are these things out there, these continuous glucose monitoring devices that will give you more data, but you're looking good. I'm not sure you're going to benefit that much from it. So, I don't think it's necessarily for everybody, but the people that Dr. Lessler included on this list, they are certainly... it's a good choice. People where... they are trying hard and they're not getting to where they want to go, people with lots of unexplained variability, and especially people with recurrent hypoglycemia or hypoglycemic unawareness where they benefit dramatically from having these, at least

in my experience, in my clinic, and I think there's reasons why you don't see that as strongly in these studies, based on how they're done.

Sheila Rege:

I wanted to kind of parse out type 1 versus type 2, because at least when I see my patients, the fact that they have to still do fingerstick at least twice a day takes away from the lure of these continuous glucose monitoring unless they have the variability or hypoglycemic episodes. Are you... so two questions. One, are you seeing a difference in the percent of your patients, and could you tell us what percent of your patients actually have this continuous glucose monitoring type 1 versus type 2, and then kind of going back to Mika's question, what are the criteria you use in your clinic of when you start talking to a patient? Is it H1c over 9, variability in hypoglycemia, do you give them what some of the insurance companies ask for, you know, a week of wearing a device to see if they have hypoglycemic episodes. So, I'd be curious about that. Thank you.

Brent Wisse:

So, in terms of percentages, it's still relatively low, certainly higher as Irl and Cate showed for the type 1 population and the type 2. I'm certainly now, for me, I'm using it more often in patients with type 2 diabetes now, especially ones that are on multiple daily injections of insulin and ones that have either a lot of unexplained variability or have had severe hypoglycemia. I think in those patients, again, the ones that respond to it, the ones that get it, and I have good luck with that. So, mostly patients that do very well. I saw a patient just today who has had lots of issues who is on a concentrated insulin, U500, and we finally managed to get her the Freestyle last month when it was approved, and her numbers have come down. It's just phenomenally in the last month and a half, in terms of her being able to figure out what she's doing with her nutrition and what she's doing with her insulin doses. So, the way I look at that is I will certainly in type 2 multiple daily injections of insulin with either high glucose with either high glucose variability or hypoglycemic events. I think the continuous glucose monitoring comes into the discussion. It's something where I will try to convince the patient that having more data, being able to take some of their unexplained variability and make it explained is going to be in their benefit. For the type 2, obviously, getting it covered has been a huge issue. Working at Harborview, most of my patient population does not have commercial insurance. So, my numbers for type 2 are much, much lower. For type 1, even, I've had issues getting continuous glucose monitoring covered for patients. So, the percentage in my clinic would be somewhere around a fifth of patients, even with type 1, that are using continuous glucose monitoring, which is low by national standards, or by what you're seeing at Children's or at the DCC.

- Sheila Rege: Follow-up question. Can you comment on the price difference, because I've heard from patients that the flash or what we have not discussed, is significantly less than the other two commercially available ones? What's the differential in price?
- Brent Wisse: I don't know if we had data on that to show. Certainly, my impression has been that it's much cheaper. I've had patients getting the flash system where they don't have, they don't need any additional test strips, or at least mostly they don't, and the cost for sensors for a month is around somewhere between \$120 or \$150 or something like that. The reader is a one-time cost, I think, of about \$80. That, I think, compares to the other continuous glucose monitoring where I think the initial startup cost is somewhere around \$1000 to \$1500. Then, the recurrent monthly cost, I think, is still in the \$250 to \$350 range for the disposable. So, from a straight cost standpoint, I think the flash system is clearly significantly less. I think even though I don't know, Abbott is not advertising it, but I think patients can go to UK websites or do something where they can actually download what they need on their smartphones rather than buying the reader. So, that's still... I've had a couple patients do that, and it saves them \$80.
- John Bramhall: Bramhall. Is there... this is a side question. Is there a reason why the flash system doesn't transmit?
- Brent Wisse: I don't know. It's just sort of the way it's set up right now is that it transmits by Bluetooth when you hold it, but it does not...
- John Bramhall: Doesn't transfer over to the space.
- Brent Wisse: ...have the bells and whistles where it has the automatic alarms and will wake the patient or alert he patient. If you're not holding the reader up to it, it gives no signal whatsoever. So, the flash system certainly for the patients with the hypoglycemic unawareness or the severe nocturnal hypoglycemia is the big issue, that's the wrong choice, but I think in the big patient population, there are lots of people that would do fine with the... or have significant improvement with the flash system that doesn't have those alerts but certainly where the hypoglycemic unawareness and the nocturnal hypoglycemia is concerned, you definitely want to use the continuous glucose monitoring that has the alerts and alarms.
- Carson Odegard: I just have a question. So, what you're saying is that, I mean, the flash being fairly new technology, so you're using...
- Brent Wisse: New to the U.S., particularly. So, much more experience in Europe.

Carson Odegard: ...so, you're seeing... so, it's more or less starting them out with the flash or the other, depending on their situation. It's not the people that are on the monitor and then wanting to transfer over to flash just because it's more convenient or less invasive, as far as.

Brent Wisse: So, I have not seen a lot of that yet, and I don't know to what extent that will happen. I think there'll be more people that would be a candidate for the flash, especially now that it looks... I mean, Medicare is covering it. The out of pocket cost to patients, even with less strong commercial insurance ends up being relatively low, and a lot of patients are going to ask for it, but it certainly isn't for everybody and, like, the patients that you heard from today that have continuous glucose monitors that communicate with their pumps or have significant nocturnal hypoglycemia, that... this group saying, hey, we're going to cover this cheaper flash and not the other things is not a solution for that subset of the patient population.

Gregory Brown: Well, if I may, the charter for this committee is to review evidence to make coverage decisions and I appreciate all the explanation and insight into this. Unfortunately, I'm not sure how we use that in our decision making process. So, I need to hear some thoughts about what people are thinking about the evidence that we have so far. The same applies... and just for the audience, I mean, the committee understands our charter to use evidence to make these coverage decisions, and the patient stories are very compelling. My mom was a type 1 diabetic. We all have our personal family experiences, it's such a common disease. At the same time, we have to make decisions based on evidence and what we're going to do for the entire State.

Seth Schwartz: This is Seth. One of the things I'm having trouble with, with this review, is that continuous glucose monitoring in and of itself doesn't change anything. It's just more data about how to treat yourself with insulin. So, there's this kind of in between step that we're missing. So, I was thinking about the pediatric data where the data was not as strong in the pediatric data that this is beneficial over continuous... over self-monitoring. I was thinking about that, as far as if someone else is administering your glucose, who cares if you have data for every minute versus if you have it intermittently, you know? It's only as often as you check it that you're going to treat it. So, I was kind of unsurprised that we didn't see as much of a benefit on the studies in the children, as we did in adults, but clearly, this is the data [inaudible] adult studies pretty much across the board we saw evidence that it has some impact but not in the longterm outcomes for A1c, less convincing as far as the hypoglycemic episodes, but there's a pretty good explanation, essentially, for why that's the case. So, I think it's

pretty evident that this technology does what it's supposed to do, which is essentially provide more data and better data about what's happening with your blood sugars, and that provides the opportunity to manage it better if you're so inclined to do so, but there's probably huge patient variability in how they're going to use this technology. So, I'm struggling with any reason why not to offer better data to patients who want to use it or need to use, or to clinicians to have that available to their patients in order to better manage this condition. So, that's kind of where I am on what we've seen.

Gregory Brown: Other thoughts?

Tony Yen: The data is pretty weak right now, and what I'm troubled by is that a lot of the information that we have before us is actually reflecting on older technology. And I don't know if it's really reflecting state of the art in the now. Perhaps, the Diamond study is the most contemporaneous, at least from what I can see with the data. I do think that this technology does offer some benefit, at least theoretically, for hypoglycemic episodes and alerting a person about a hypoglycemic episode. Unfortunately, it's not really very clear by the actual analysis of the data. So, though intuitively, it makes sense, what we have in the analysis before us is not really entirely clear.

Gregory Brown: This is what we have to make our decision with.

Sheila Rege: This is Sheila, and I am leaning towards what Tony is talking about. I think the data doesn't prove it, but it seems like it's most useful for hypoglycemia, severe hypoglycemic episodes, especially nocturnal, but the data is weak.

Gregory Brown: So, maybe I have a different question that I don't think was addressed in the report, and that is, is how frequent is a coma or a death from hypoglycemia? I mean is it in one in a million, one in a thousand, one in?

Brent Wisse: That's something where the better the control you achieve over diabetes with insulin, the more frequent it's going to be. Irl showed a slide of sort of the incidence of hypoglycemic associated mortality but also severe hypoglycemia. And the longer the duration of the diabetes, and the better the control, the more you're going to have... the more hypoglycemia and the more hypoglycemic unawareness that you're going to have. That being said, overall, the rate of death from hypoglycemia is low, but always comes within an asterisk, especially in our patients that are the greatest risk, which is the type 1 patients that have had diabetes for more than 20 years, and if they wake up dead, right, you don't know why they woke up dead.

And you kind of say, well maybe they had a heart attack, right? Somebody... does this mean they had a stroke. It's often hard to sort of say this was a death caused by hypoglycemia.

Sheila Rege: I did pull up the study from Yale about hospitalization rate for hypoglycemia and the increase. I don't know if you have any comments about it being increased that you have seen in your literature. Is that something we're seeing increased, as we start to really get the A1c under control, hospitalizations?

Brent Wisse: So, the hospitalization rate from hypoglycemia, it definitely varies in studies, depending on what the sort of parameters are. In Seattle, the rates are relatively lower, just because our Medic One teams and our paramedics are actually fairly comfortable keeping people at home and monitoring them and starting IV and giving dextro. So, there's a lot of people with severe hypoglycemia that don't get brought to the hospital, because they get rescued at home. So, the rates definitely vary based on that practice. So, it's kind of hard to compare from one place to the other and one country to the other.

Mika Sinanan: Mika Sinanan. My sense is that the preponderance of the data shows either moderate or good benefit. No study showed a adverse outcome from this. That, for the reasons that I think Seth raised about it being more information and not an intervention, there are other aspects about translating this into a clinical improvement that are social, clinical, informational, communication, cultural that have to be addressed at the same time. The horse is out of the barn. Whoever is on the phone, we're hearing you. If you could mute, that would be great.

Gregory Brown: It's already muted. Yeah.

Mika Sinanan: Alright. Well, there are mice in the walls then. So, the horse is out of the barn with regards to whether this is going to happen. It's happening, and it's happening around us and will continue to progress, as we have heard. I think we want to be very careful about not giving essential information to those patients and providers who will use it and will extend their live, improve the quality of their life, and reduce morbidity in the longterm. That's a subset of the total group. So, really, the question is, as I think Dan had summarized in his slides is, support, but what are the conditions under which we support it. Who are the... what are the right subsets of patients. What are the right criteria for entry that we need to set, not is it... should we do it or not do it. It's more a matter of who, and part of my earlier question was, this is obviously a moving target. One of the limitations of all these studies is, by the time the study is done, the technology has

moved on to the next phase, and those studies will always be potentially criticizable, because, well, they didn't use the newest technology, and we can now do this, but that's true of all technology evolution. So, the preponderance of the data supports that there is efficacy. I think the safety is good safety. If there are skin reactions and a few allergic reactions, but it's not major high risk events, and I have to say, personally, if you can save one life, that's a wonderful thing from an avoidable problem. That's a wonderful thing.

Seth Schwartz: This is Seth. I would just have one more comment about the technology issue. We were told explicitly that they did not look at any of the studies that included the therapeutic interventions. So, presumably, there's some device that can also react to the data that's provided by continuous monitoring to actually basal glucose, or basal insulin at the same time. That's kind of fascinating to me, and I'm not... I know it's not part of this review, but it seems like that type of technology, which seems like it's happening, would not be possible without blood glucose monitoring. So, I worry... I certainly don't want to restrict access to that if that technology is going to evolve quickly and become accessible to people, because that seems, I mean, and I value your opinion. It seems like that may be the future of this whole field is, if you can have realtime detection of what your glucose levels are in realtime management, that's going to lead to the safest and closest management.

Brent Wisse: That's correct. On a pump, you can change the basal settings just knowing sort of changes in somebody's blood sugar based on point of care measures or knowing changes in physiology. So, that part already gets you off in a significant part of the way there, whereas the actual closed loop monitors where the feedback from the continuous glucose monitor is adjusting the basal rate, still improves on that and takes that sort of up a notch in terms of the basal insulin administration. So, yeah. That is certainly something where dialing that down will, again, improve the overall glycemic control.

Gregory Brown: Are we ready to look at our tool? Okay. Actually, let's do that. We want to... are we supposed to talk about our other coverage decisions and guidelines or clinical practice guidelines before we do our voting typically?

Josh Morse: No. We typically check on that after we've made our decision.

Gregory Brown: Okay.

Josh Morse: Thank you.

Gregory Brown: Okay. So, safety issues. Dr. Walsh, we're off mute?

Kevin Walsh: I'm wondering if it makes sense for us to look at type 1 and type 2 as two separate groups, as we start to look at safety and efficacy issues. I'm asking that, because clinically, I think of them as two different groups of patients, and the disease seems to respond differently. So, for me, that makes sense, but I don't know how other people feel.

Gregory Brown: And do we also want to include pregnancy as a separate group? I mean, I have to say, in terms of outcomes, NICU days and C-sections, this is some of the most compelling outcome data we have.

Kevin Walsh: So, the pregnant women with diabetes are broken into type 1, type 2, and gestational. So, it makes... we could discuss pregnancy... I mean, really, we're talking about six different categories here, type 1 three categories, type 2 three categories, children, adults, and pregnant women.

Gregory Brown: I'm an orthopedist, so I'm out on a limb, and I know you now have extremely obese children that have some type 2 diabetes, but I think that's extremely rare, isn't it?

Brent Wisse: Sadly, no. It's not that rare.

Gregory Brown: Okay.

Brent Wisse: And I think in terms of the distinction, I'm not sure it really gets you that far. In fact, there's lots of... there's type 1.5. There's type 3. I mean, there's all kinds of, if you want to start getting fancy. And I think it's something where to me, the better way to think about this is, if somebody who is taking insulin multiple times a day has a significant hypoglycemia risk or has significant glycemic variability that's unexplained, whether they're type 1 or type 2 or pregnant, doesn't really matter that much. It's just sort of... it's what's going on with their blood sugars that's contributing to their risk profile that sort of really sets the likelihood of them benefiting from this technology.

Kevin Walsh: I can accept that. I'm looking at the NICE guidelines in the report, which, to me, makes the most sense, because they do break down... I mean, they do have a filter saying that this is most relevant for people who have hypoglycemic episodes or who have lost hypoglycemic awareness. They have some caveats to using it. So, I don't want to push the discussion further than everybody else, but I think we do have some guidelines to look at that might support what you are advocating.

- Gregory Brown: Kevin, what page are you on, just for... so we're all on the same... for the?
- Kevin Walsh: I think it's page 98 in the report, but I'm not sure. I'm having... I just lost it on my computer.
- Josh Morse: So, there's a decision tool in each of your binders, and we excerpt the guidelines table. The complete information is in the report.
- Gregory Brown: Okay.
- Josh Morse: And you have printed copies of the report. I realize I'm off mic here. Here's a few copies.
- Gregory Brown: Oh, yeah. I've got a copy if anybody needs to see it.
- Kevin Walsh: I'm sorry. It's page 30 of the report. Yeah, I'm looking at the P-, at the final report.
- Josh Morse: He's looking at the final report, but in your binder in the decision analytic tool, you'll see, that's taken right from the report, and it's just a summary table.
- Sheila Rege: This is Sheila. This makes logical sense. It's just that I'm not sure the data supported it, and that's what our expert also concurred with that being an important need.
- Gregory Brown: There's nothing here on women with pregnancy, or gestational diabetes.
- Sheila Rege: I would be fine considering type 1 versus type 2 versus gestational differently, as three categories, or do you want more? Or what our expert said, just all of them with?
- Gregory Brown: I think the previous recommendations have split out children versus adult versus pregnancy, because previously it was just adults, right, no kids? So, was it reverse? Okay. I guess, then, the other question is, is it type 2 or only type 2 on insulin. I mean, it sounds like typically the benefit is if they're on insulin, 'cuz if they're on oral hypoglycemics, it's different risks.
- Brent Wisse: So, I think it's, the bias in my practice is, I try to use medications that minimize the hypoglycemic risk, as much as possible, as long as possible in those patients, and there's lots of medications that do that in type 2. So, it's mostly the patients on insulin where I am considering continuous glucose monitoring for those patients. It's not a perfect characterization, but it certainly would cover the majority of them.

Gregory Brown: Okay. So, our three categories, I'm hearing, are pediatric, adult type 1, adult type 2 on insulin, and then pregnancy. So, we're having four categories? Is that? Everybody concurring? Nobody's disagreeing?

Seth Schwartz: I mean, there are four categories. Do we have to separate them into four categories is a different question.

Gregory Brown: I guess my thought process, at this point, I'm thinking about them separately. So, okay. So, we'll talk each four categories... I mean, they may not have had safety issues or whatever, but I think they have different effectiveness. Okay. So, we'll go to our tool. The first one is safety. So, we've got morbidity from the devices, itself, which were basically sensor issues primarily is what it sounds like. I'm still fighting macrosomia from my mom who was a type 1 diabetic. So, is that another safety issue?

Brent Wisse: And that applies to all four categories.

Gregory Brown: Yeah. It's device dependent, not the patient, I think.

Brent Wisse: When you discount that one episode of retinal detachment, which is [inaudible].

Gregory Brown: Yeah. I think that's an FDA reporting issue as any event that happens while they're in a trial. They have to report. Then, you also grade it as to whether you think it's likely related, and I think we're all saying we think it's very unlikely that that's related to the device. So, okay. So, we will vote for safety, whether we think that... so, I guess the compare... so, what are the key factors and health outcomes and what evidence is there for the populations. So, does anybody think there's a difference in population groups here? So, does it matter? No? Okay. So, we'll vote once. Then, the comparison would be continuous glucose monitoring versus self-monitoring.

Brent Wisse: Recognizing that they have to do some self-monitoring to calibrate.

Gregory Brown: Except the flash.

Brent Wisse: Except the flash.

Josh Morse: So, this is [inaudible]. Did everybody vote for safety? I see one, two, three, four, five equivalent, three some, and Dr. Walsh?

Kevin Walsh: Equivalent.

- Josh Morse: Six equivalent. Thank you.
- Gregory Brown: Okay. Efficacy and effectiveness. I think this one we do need to split up, start with pediatrics. So, review of the tables basically... the main differences I saw on the studies depending on the time points were decrease in hemoglobin A1c or attaining hemoglobin A1c less than 7, and in kids, did we see a difference?
- Carson Odegard: Greg? Yeah. I'm thinking we could jump ahead and do cost-effectiveness for all three, because we can group them together? Would that be a possibility? Then, we can spend our time...
- Gregory Brown: Well, I guess if I don't think it's effective in kids, but I think it is in adults, how can it be cost-effective for everybody? Or did I say that wrong?
- Carson Odegard: That's my thinking, too. Yeah. Right. So, it could be a quick decision.
- Gregory Brown: I don't know how to split that one, I guess, is what I'm saying.
- Carson Odegard: Yeah.
- Gregory Brown: The others? Okay. So, we don't have anything for kids. So, okay. Nothing in pregnancy for cost-effectiveness. So, cost-effectiveness, then, for adults, type 1 or type 2 with insulin. Do we think it's cost-effective?
- Josh Morse: One, two, three, four, five, six unproven, two some, and Dr. Walsh?
- Kevin Walsh: Unproven.
- Josh Morse: Seven. Thank you. Seven unproven, two some.
- Gregory Brown: Okay. So, back to efficacy and effectiveness. We're good. Should we start with pediatrics? So, if I remember, at three months there may have been a small difference, but by six months or a year there really wasn't any differences. Does anybody see the evidence differently?
- Laurie Mischley: I'll add that, this is Laurie, the small kids are noncommunicative about hypoglycemia, and I think that's relevant.
- Gregory Brown: Okay.
- Seth Schwartz: This is Seth again. When we see the summary slides for the A1c at a year, it actually is significant. It's just on the very border of that. They're an

accumulative estimate. I mean, it's barely, but it's... it favors continuous glucose monitoring. Slide number 20.

Brent Wisse: The real world data that Cate showed also looked much better. The current one from the type 1 diabetes exchange and from their studies with children looks better than the ones based on the old technology that were included in this.

Tony Yen: Are we allowed to consider the evidence in this booklet or?

Gregory Brown: No.

Tony Yen: Or we're allowed to consider also the evidence presented by Children's?

Gregory Brown: Yeah.

Tony Yen: Okay.

Gregory Brown: If it's appropriate evidence and weighted accordingly, yeah.

Kevin Walsh: The evidence presented by Children's? Excuse me?

Gregory Brown: I'm sorry. The pediatric endocrinologist that... is she still here? Who was it?

Brent Wisse: Cate Pihoker is the senior endocrinologist or the head of endocrinology at Seattle Children's and a big type 1 diabetes specialist in kids.

Gregory Brown: Well, could you summarize?

Brent Wisse: So, the data she showed was improved A1c in children on continuous glucose monitoring versus not. The difference between the children that were using continuous glucose monitoring and the ones that weren't varied between sort of a 1% and a 0.7 or 0.8% difference by different ages. She had them broken down, less than 6, 6-13, greater than 13. So, the data was that with continuous glucose monitoring, they had lower A1c than without continuous glucose monitoring.

Gregory Brown: So, that's observational data. It's at a single institution in this State. So, one of the issues we always... is it just from Seattle Children's, or is it national data?

Brent Wisse: She presented both, if I remember. It was both the national... it was her Seattle Children's, but also the national data from the big observational study called the type 1 diabetes exchange.

Kevin Walsh: I'd like to ask a process question.

Gregory Brown: Sure.

Kevin Walsh: Historically, we've limited our consideration to the material that we were presented. I feel like if we want to make a change in that, that's a process change in the way that we come to a decision.

Gregory Brown: Well, actually...

Kevin Walsh: Josh, can you weigh in on this?

Gregory Brown: ...I'll make a comment first, Kevin, and then... if I remember one of the spinal reviews, some of the presentations provided... reported on clinical trials that were not in the evidence review, and we considered them. Again, it's up to the committee to weight them, observational versus randomized control trial and everything, but I don't... again, it doesn't say in our charter that we can't... we can only look at what's in the evidence report.

Josh Morse: Your charge is to evaluate the evidence that you're provided with and put the greatest weight on the evidence provided by the evidence vendor. It doesn't exclude you from considering other information that's been presented to you, but the greatest weight would go on the evidence report. That's the mandate that you're charged with.

Gregory Brown: Okay.

Kevin Walsh: Thank you.

Gregory Brown: So, I don't know. I would like a little discussion here on how people are weighting that and what they're thinking. Again, I don't... thoughts?

Tony Yen: I find the Seattle Children's data to be compelling actually, but it seemed to be inconsistent with what we are provided.

Gregory Brown: So, this is an issue of... just like there's not a good way to look at crossover studies, randomized control trials, my national society, we try to understand how to include registry data, because things like safety or prognostic factors are very hard to find in a subgroup analysis and an RCT.

So, we often feel that observational data may be the best evidence, but we feel like our hands are tied by the grade mechanism, the grade approach to evidence. So, again, we all individually have to do this, but I would like some discussion.

John Bramhall: I think you're right. We did attract some criticism on one of the spinal studies about not using I think it was scope data was the specific data set that was being introduced. We did have criticism that we weren't incorporating those data effectively enough. That's my recollection.

Gregory Brown: Well, no. I agree with you. There is scope data, but that, actually, there was never any scope data presented.

John Bramhall: Right. So, my...

Gregory Brown: So, but there was, I think it was on the spinal injections one, there were some other randomized control trials that one of the other public... I think it was a physician in the public comments said that this trial was left out of the evidence review, and they didn't feel that that was appropriate. So, in a situation like that, if there's missing evidence, quote unquote, and it's brought before us, I think we can certainly consider it.

Carson Odegard: There was an example, and Josh would remember this. Spinal surgery where we had some discussion about one of the major papers, one of the major trials. And we were confused, but we were fortunate enough to have the principal investigator sitting in the audience and could comment on the actual trial itself, and that was very important.

Josh Morse: Right. So, I guess what I would say is...

Kevin Walsh: But that's different...

Josh Morse: ...oh, go ahead and Dr. Walsh.

Kevin Walsh: ...that's different than new material, Carson. I have a problem with somebody's presentation of a study at the moment without a chance to look at... to verify their interpretation of the study, myself. If somebody can make a compelling, charismatic case at the podium, that... I don't feel comfortable with that.

Mika Sinanan: Yeah, Mika Sinanan here. If the data that is presented at the time runs significantly counter, 90 degrees or 180 degrees from what the rest of the data shows, I entirely agree with that, but it didn't. All it did was show that in a subpopulation at Children's, and obviously a very select

subpopulation, just getting there and getting into the clinic, they're select patients. They were able to show substantial benefit, the scale of which appeared to be greater than what we see in the other reported studies, but the trend was the same direction. Is that right?

Josh Morse: So, you have the slides from the Children's presenter in your binders, and they are in the meeting materials online, Dr. Walsh, if you want to refer to them. I would also suggest you have expertise from aggregate analytics that could tell you how they would grade this information if you're interested in that perspective.

Kevin Walsh: Could I make... I'm not disagreeing at all with the thrust of that finding. I'm just introducing a process question, and if people don't have a problem with that process, I don't want to stand in the way of it, but I'd like to make a clinical observation. For me, the strength of proof for children with type 1 diabetes, I would accept less strength of proof than for adults, and the reason is because they have 60, 70 years to live with this disease, as opposed to a 65-year-old adult with type 2 diabetes. So, that's why I think of them as different situations. So, I'm willing to accept less strength of evidence when I'm thinking about children with type 1 diabetes than I am with adults with type 2.

Gregory Brown: Okay. Are we ready to vote then for pediatrics? So, in the pediatrics subgroup, is there sufficient evidence that the technology has a meaningful impact on patients and patient care?

Josh Morse: I see eight some, and Dr. Walsh?

Kevin Walsh: Some.

Josh Morse: Nine some.

Gregory Brown: Okay. Then, same question for adults with type 1 diabetes.

Josh Morse: Eight some. Dr. Walsh?

Kevin Walsh: Unproven.

Josh Morse: One unproven, eight some.

Gregory Brown: Type 2 diabetes on insulin.

Josh Morse: Type 2 insulin. Okay. One, two, three, four, five, six some, two unproven. Dr. Walsh?

- Kevin Walsh: Unproven.
- Josh Morse: Three unproven and six some. Okay.
- Gregory Brown: And then pregnancy.
- Josh Morse: Eight some.
- Kevin Walsh: Unproven.
- Josh Morse: One unproven.
- Gregory Brown: Okay. Okay. So, we have done safety, cost-effectiveness, cost outcomes, effectiveness, and efficacy effectiveness. Okay. So, summary is essentially equivalent on safety, six to three.
- Josh Morse: Equivalent, yep.
- Gregory Brown: And in terms of cost-effectiveness.
- Josh Morse: Seven unproven, two some.
- Gregory Brown: So, essentially, no information. An efficacy all groups, some had the majority.
- Josh Morse: Majority are landing in some.
- Gregory Brown: Okay. So, I think we're leaning towards coverage with conditions. So, we're ready to go after the conditions. And then, the question is, do we want to start with the State's recommendations? Do we want to do our own? Sheila, you're shaking your head. Do you want to do our own? So, I'll let you...
- Sheila Rege: I agree that the NICE recommendations is a good starting point. We can add from the State, maybe? Is that allowed?
- John Bramhall: With the NICE recommendation, it includes, and I actually approve of it, but it's a separate issue, a pretty subjective element, which is a fear of hypoglycemia. That's not really very objective, and you can imagine a counseling situation where someone who wants this technology says I'm really frightened of hypoglycemia, and I don't object to that as an element, but it's an interesting subjective component.

- Gregory Brown: I think some of the patients that spoke, if you live alone versus you have a child with you and that's the only person with you, that's a very different environment than if you're married and don't travel and are always with your spouse.
- Carson Odegard: When a physician tells you that you have to live with somebody else. That would put the fear in you.
- Sheila Rege: I'd be interested in what our expert says on that. Do you hear that with patients when, I mean, would you use that? Would you say that's reasonable?
- Brent Wisse: It's something not well studied, and there's something inimical about hypoglycemia that really is probably neurochemical that puts fear into people. So, it's actually not uncommon to have people that will not take insulin with meals either ever or appropriately, just because of that fear of hypoglycemia.
- Mika Sinanan: I would just comment that my understanding of the hypoglycemic symptoms are the same types of symptoms you have when you're dying. It is an epinephrine surge to mobilize glycogen, tachycardia, sweating, not at all a mystery why people don't want to go through that.
- Sheila Rege: But is that, is that something that anybody could say they were really afraid? Do they need to have one episode of hypoglycemia? I mean, I think that's what John was asking. It's just a little ambiguous.
- Kevin Walsh: I agree.
- Gregory Brown: So, the first condition is greater than one episode of severe hypoglycemia per year with no obvious preventable precipitating cause. So, we agree on that?
- Sheila Rege: I think I'm good with that. I mean...
- Gregory Brown: Okay.
- Sheila Rege: ...unless the expert says that's, you know?
- Gregory Brown: We're on, yeah. We're on NICE page 12 in the summary. So...
- Sheila Rege: Are these ands or are these ors?
- Gregory Brown: Or. Do you have a question or a comment, Seth?

- Seth Schwartz: I'm just wondering in clinical practice, do you almost universally start people on other forms of monitoring before you would go to continuous glucose monitoring, like, in a child, I guess, is what I'm really thinking about. Or would you... might you offer this to somebody directly?
- Brent Wisse: It would be unusual.
- Sheila Rege: Maybe we should ask if others want to start with the NICE or with what we had presented, which is, NICE, but maybe we should look at the agency directors'.
- Mika Sinanan: I actually like the agency director's recommendations.
- Gregory Brown: Okay.
- Mika Sinanan: They're pretty simple, and they actually kind of replicate a lot of what the previous professional societies recommend, as well.
- Sheila Rege: And do the same for all, which is the same for all categories.
- Kevin Walsh: Except for pregnant women. They're covering all pregnant women with type 1. The caveats are for pregnant women with type 2, I think.
- Sheila Rege: So, should we do them separately or just take the first three as the same and... I mean, what I heard was severe hypoglycemia, unexplained variability, and taking insulin multiple times a day from our expert as.
- Gregory Brown: So, on the type 2, they don't make the distinction of with or without taking insulin.
- Sheila Rege: I think I heard insulin multiple times a day for all of them, though, correct?
- Kevin Walsh: Yeah. Both of the caveats, the first two caveats with adult with type 2 described intensive insulin therapy.
- Sheila Rege: Okay.
- Kevin Walsh: So, I think Sheila is right. We can take the first... we can think of children with type 1, adults with type 1, adults with type 2, and apply the same criteria. We're only adding universal coverage for women who are pregnant with type 1.

- Sheila Rege: And there's a question for the expert. Would this recommendation prevent or help the discussion with the patient who wants this, or would it have everybody wanting to do continuous glucose monitoring? Do we have enough explanation in there of who it's good for?
- Brent Wisse: I think it's a very reasonable explanation. I think... there will be lots of patients who don't want to do it, even some of them, unfortunately where they would be great candidates for it. So, I don't think these recommendations would encourage overuse, if that's the concern.
- Gregory Brown: But does it prevent people that need it from getting it was the other question.
- Brent Wisse: The only category that I'm thinking of is that there are people that just... if the criteria of testing blood sugar four times or more a day is too strict, that would leave some of my patients out, because there are some people where I just cannot get them to test, period, or more than once a day. They clearly have hypoglycemic episodes, and they can be very hyperglycemic at times, just from a random scatter shot of data over a month.
- Gregory Brown: I guess my concern is if they won't do it even once a day, they can't calibrate their continuous glucose monitor.
- Brent Wisse: Right, but then that would be... those are the patients where the flash would be better for them.
- Gregory Brown: Right.
- Sheila Rege: And is there something here, I know we've... in our data we've not looked at flash. Is that something we clarify or... that it wasn't looked at. I'm not sure how we...
- Gregory Brown: Well, I...
- Sheila Rege: ...how they...
- Gregory Brown: ...guess I've been trying to figure that out. I don't think we want to... in our... my thoughts and, Dr. Lessler, you might comment, but given this technology is changing so quickly, I don't know that we want to specify specific devices within this recommendation. You still have the option of what devices you would cover, don't you, I mean, in terms of, I mean, the fact that you cover something doesn't mean you cover anybody that has something approved or on market. I don't... that's a question.

Dan Lessler: It doesn't mean we cover everything that is on the market, but we would... you can have multiple devices that are essentially the same, and we would have the choice then of which one we would cover. I'll be quite... I struggled myself with separating the flash from the others. What I would say is, while the recommendation based on the evidence, there is not as much evidence around it. My own thinking about that was because it doesn't alarm. So, it's not going to really be useful for the hypoglycemic indications that are built into our recommendation, and there is some limited evidence. I think the vendor said it was inadequate. I can't remember your... insufficient. I can't remember how you classified that, but what was there did, just on its own merits, suggest some degree of benefit. I can't remember whether it was out the six months or three months or what it was. So, I will honestly say I think we struggled with that. I don't think it's unreasonable to go in the direction where it's just... you just cover it regardless of the type. Administratively, it makes it easier for us, but I think it's good that it's just explicitly discussed in terms of the differences of data that's available.

Gregory Brown: I guess, I'm trying to understand why flash doesn't alarm. I'm guessing one of the reasons is because one of the reasons that people discontinue the older technology is because they don't like the alarming. So, then, Okay. We'll give you one without alarms, but at the same time, I'm seeing a shaking no, but, okay. I guess the issue is, if you could put an app on your phone...

Sheila Rege: Which you can in Europe, it sounds like. And the other thing is, they don't have to stick themselves anymore.

Gregory Brown: ...right. So...

Sheila Rege: So, I think... I think leaving it to the physician's discretion.

Gregory Brown: ...yeah.

Brent Wisse: You could say that if the main driver behind you prescribing this is, hypoglycemia, unrecognized, unawareness, nocturnal, then the flash is not the way to go. You want to go with traditional continuous glucose monitoring, but if that's not the main indication, and if they do Okay with the... if they have... if they can benefit from the flash system, presumably that would be much less expensive for the State.

Gregory Brown: And I think the clinician is going to help the patient decide that, right? Yeah. Okay.

- Mika Sinanan: So, a question, about people who already are using continuous glucose monitoring, but haven't had, because of their continuous glucose monitoring, hypoglycemic episodes, do they become ineligible?
- Brent Wisse: Historically, what we've done is, those people are effectively grandfathered, if they predated the decision and so forth. So, there would be no problem there.
- Gregory Brown: Okay. So, we have one, two, three, and basically we have the same recommendations that the State gave us. Okay. And then, we're also adopting for the pregnant women with diabetes. We're taking those four points.
- Carson Odegard: Unless you want to split those up and put them under type 1 and type 2.
- John Bramhall: This should probably be pregnant women taking insulin prior to pregnancy versus those, right. That's the easiest split, if we are splitting. So, it's universal... the suggestion is universal coverage for any pregnant woman who is diabetic of any sort who was taking insulin, right, through pregnancy, and then the separate one is the conditional.
- Gregory Brown: You've got it. You're either type 1 diabetic on insulin, or you're a type 2 on insulin, so. I mean, I guess to me, it's easiest to leave those to the pediatrics, adult type 1, and adult type 2, and then pregnant women as no modification to the state recommendations.
- Sheila Rege: And no definition of target H1.
- Gregory Brown: And I think that, you know...
- Sheila Rege: Up to the clinician.
- Gregory Brown: ...we'd be changing clinical practice guidelines. There's all sorts of things. So, I think that's... that the clinicians will work that out.
- Seth Schwartz: And what's changing is that the last slide, because Dan, you had continuous glucose monitoring with a flash device is not covered, but now we are putting flash... or the goal... or your recommendation is to put flash in there now or not?
- Gregory Brown: We're not drawing any distinction. We're just saying continuous glucose monitoring, whichever technology. Okay. Any comments, Kevin? I can't see you shaking your head. Everybody else I can see, so.

- Kevin Walsh: No. I'm supportive of this.
- Gregory Brown: Okay. Then, we are going to vote on cover, cover with conditions, or not cover.
- Josh Morse: I see eight cover with conditions.
- Kevin Walsh: And I agree.
- Gregory Brown: We're unanimous.
- Josh Morse: Nine cover with conditions. Let's answer the question about National Coverage Determinations.
- Gregory Brown: National Coverage. So, Medicare is covering with conditions. So, we're certainly consistent with that.
- Josh Morse: So, your decision guide shows that you don't have a National Coverage Determination.
- Gregory Brown: Right, but there is a way to get durable medical equipment. So, I think yes. It's complex, I think was the explanation earlier during the presentation. So, although there is no National Coverage Decision, there is a way to get this as durable medical equipment. So, we're consistent with that.
- Josh Morse: Okay.
- Gregory Brown: And the clinical practice guidelines, certainly a number of them recommend it. So, we're consistent in terms of having conditions for which, you agree? Okay. Thank you to our presenters today, and thank you for all your time. Then, I think we have just a few minutes for some updates.
- Josh Morse: We do have a couple updates. So, I would invite you to turn to the back of your binder. There are draft key questions for a topic that is out. The topic is pharmacogenetic testing for patients treated with anticoagulants. This is currently scheduled for a review at your meeting in May. This is an opportunity where you can review the draft key questions and provide feedback, either now or in the next few days. The comment period closes on the 22nd.
- Gregory Brown: Okay.
- Josh Morse: Anything else, sir?

Gregory Brown: That is it.

Josh Morse: I would say, related to your next meeting and information that will be coming out from Dr. Brown and from program staff is about the bylaws. So, we are working on just administrative updates due to some rule changes and other changes from a year and a half ago, and between now and March, we hope to have a draft ready for review by you, outside of meeting, have a public comment opportunity in that period, and then have discussion at the March meeting. There is only one topic scheduled for the March meeting right now, and we hope to have the bylaws on the agenda for after that review, if that's okay with everybody. Okay.

Gregory Brown: Okay.

Josh Morse: I will finally say that this was only recently confirmed, but Dr. Elmore has left the committee. So, we do have a vacancy, and we will be initiating recruiting for that position and continue recruiting for Dr. Odegard who has graciously agreed to stay until we identify a successor, per the rules. And additionally, Chris Hearne is taking some leave, and that's why he is not here today. He'll be missing a couple of meetings this year. He is away for a bit. Okay. That's all I have, unless you have questions for me.

Gregory Brown: Thank you.

Josh Morse: Okay. Thank you, very much.

Gregory Brown: Thanks all.